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Peer Reviewer of *World Journal of Critical Care Medicine*, Athanasia Papazafiropoulou, MD, MSc, PhD, Attending Doctor, Research Scientist, 1st Department of Internal Medicine and Diabetes Center, Tzaneio General Hospital of Piraeus, Piraeus 18536, Greece. pathan@ath.forthnet.gr

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EDITORIAL

Cough as a neurological sign: What a clinician should know

Mohammed Al-Biltagi, Adel Salah Bediwy, Nermin Kamal Saeed

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Mohammed Al-Biltagi, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Manama 26671, Bahrain

Mohammed Al-Biltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31512, Al Gharbia, Egypt

Mohammed Al-Biltagi, Department of Pediatrics, University Medical Center, Dr. Sulaiman Al Habib Medical Group, Manama 26671, Bahrain

Adel Salah Bediwy, Department of Chest Disease, Faculty of Medicine, Tanta University, Tanta 31512, Alghrabia, Egypt

Adel Salah Bediwy, Department of Chest Disease, University Medical Center, King Abdullah Medical City, Arabian Gulf University, Manama 26671, Bahrain

Adel Salah Bediwy, Department of Chest Diseases, University Medical Center, Dr. Sulaiman Al Habib Medical Group, Manama 26671, Bahrain

Nermin Kamal Saeed, Department of Pathology, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, Manama 26671, Bahrain

Nermin Kamal Saeed, Department of Pathology, Irish Royal College of Surgeon, Busaiteen 15503, Almuharraq, Bahrain

Corresponding author: Mohammed Al-Biltagi, MBChB, MD, MSc, Chairman, Professor, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Building 61, King Abdelaziz Avenue, Manama 26671, Bahrain.
mbelrem@hotmail.com

Abstract

Cough is a common respiratory complaint driving patients to seek medical advice. Besides being a fundamental respiratory sign, it is also a crucial neurological sign. There are three main types of coughs: Reflex cough (type I), voluntary cough (type II), and evoked cough (type III). Cough is a reflex predominantly mediated by control centers in the respiratory areas of the brainstem, modulated by the cerebral cortex. Cough reflex sensitivity could be increased in many neurological disorders such as brainstem space-occupying lesions, medullary lesions secondary to Chiari type I malformations, tics disorders such as Tourette's syndrome, somatic cough, cerebellar neurodegenerative diseases, and chronic vagal neuropathy due to allergic and non-allergic conditions. Meanwhile, cough sensitivity decreases in multiple sclerosis, brain hypoxia, cerebral hemispheric stroke with a brainstem shock, Parkinson's disease, dementia due to

Lewy body disease, amyotrophic lateral sclerosis, and peripheral neuropathy as diabetic neuropathy, hereditary sensory and autonomic neuropathy type IV, vitamin B12, and folate deficiency. Arnold's nerve ear-cough reflex, syncopal cough, cough headache, opioids-associated cough, and cough-anal reflex are signs that could help diagnose underlying neurological conditions. Cough reflex testing is a quick, easy, and cheap test performed during the cranial nerve examination. In this article, we reviewed the role of cough in various neurological disorders that increase or decrease cough sensitivity.

Key Words: Cough reflex; Neurological disorders; Cerebral disorders; Cerebellar disorder; Vagal neuropathy; Parkinsonism

Core Tip: The article aimed to define the role of cough as a crucial symptom and sign for various neurological disorders. It sheds some light on the cough reflex and when its sensitivity is exaggerated or depressed and related to multiple neurological diseases. Cough reflexes can help diagnose some acute and chronic neurologic disorders, both in children and adults.

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INTRODUCTION

Cough is a forced expiratory effort against a closed glottis that opens suddenly with the expulsion of secretion and foreign particles out of the airways, producing a distinctive sound. Cough is one of the most common complaints driving patients to seek medical advice. It is one of the essential respiratory protective mechanisms, alerting to the presence of a potential or actual respiratory tract lesion, and helps to clear secretions and foreign particles from the airways[1]. There are three main types of coughs according to the central control mechanisms: Reflex cough (type I), voluntary cough (type II), and evoked cough (type III), which follows the urge to cough[1,2].

Both reflex and voluntary cough initiate similar mechanisms of cough motor behavior. Cough is a reflex predominantly mediated by control centers in the respiratory areas of the brainstem, modulated by the cerebral cortex (Figure 1). Cough production passes through three harmonized phases: Inspiratory, compression, and expiratory. It starts with contraction of the inspiratory muscles (drawing air into the lungs), closure of the glottis (which generates a subglottic pressure), and abduction of the vocal folds with a forced expiration (enforcing the glottis to open) with expelling of the secretions out. However, the cough reflex is under the voluntary control of the higher neurologic centers, such as the cerebral cortex, which has a vital role in initiating and inhibiting cough[3]. The reflex has afferent sensory nerve fibers (mainly branches of the vagus nerve), which carry the afferent impulses diffusely to the medulla to reach the upper brain stem and pons. Other brain parts are integrated with the proper function of the cough center in the medulla as the pontine respiratory group, the lateral tegmental field, and deep cerebellar nuclei, which play a role in the pattern of cough generation, and regulation. The efferent fibers carry the signals from the cough center *via* the vagus, phrenic, and spinal motor nerves to the diaphragm, abdominal wall, and muscles[4]. As the cough reflex is a reflex, it could affect or be affected by different neurological disorders (Table 1). Both reflex and volitional coughs could be tested in various neurological and otolaryngological conditions. Other methods can test the sensitivity and efficiency of the cough reflex. The sensitivity can be assessed by the concentration or the duration at which the cough can be evoked when exposed to variable concentrations and/or durations of nebulized aerosols of a tussive substance (such as citric acid, L-tartaric acid, or capsaicin). However, considerable variabilities in the used methods are present while performing the test[5-7]. A group of Japanese scientists developed a device to measure cough strength while testing the cough reflex to assess cough efficiency and strength. They added an electronic spirometer to an ultrasonic nebulizer through a special pipe with a double lumen. The spirometer measures the peak cough flow of the provoked involuntary cough[8].

Table 1 Neurological conditions associated with increased cough reflex sensitivity and its mechanism

Disorder		Mechanism
Cerebral disorders	Psychogenic causes: Somatic or "tic" cough, Tourette's syndrome	(1) Peer and familial psychosocial stress; and (2) Mediated in part by the dopaminergic activity
	Primary central reasons: (1) Medullary lesion: Chiari I malformations; (2) Space-occupying lesion; and (3) Neuromyelitis Optica spectrum disorder	(1) Lesions in the dorsal medullary region of the brainstem; (2) Irritation of the cough center; and (3) Autonomic dysregulation secondary to loss of parasympathetic innervation
Cerebellar disorders	Cerebellar neurodegenerative disorders *e.g.*, autosomal dominant cerebellar ataxia	Lesions in deep cerebellar nuclei which are engaged in neural activities necessary for breathing and coughing causing laryngeal hyperreactivity and vagal dysfunction
Vagal neuropathy	Viral infections	Induction of persistent plasticity in the neural pathways mediating cough with activation of the cough-evoking sensory nerves that innervate the airway wall
	Irritant exposure	Irritation of the rapidly adapting irritant receptors, located mainly on the posterior wall and the carina of the trachea, and pharynx
	Chronic conditions such as asthma	Due to Airway vagal hypertonia
	Vitamin B12 deficiency	Damages the myelin sheath and axonal degeneration

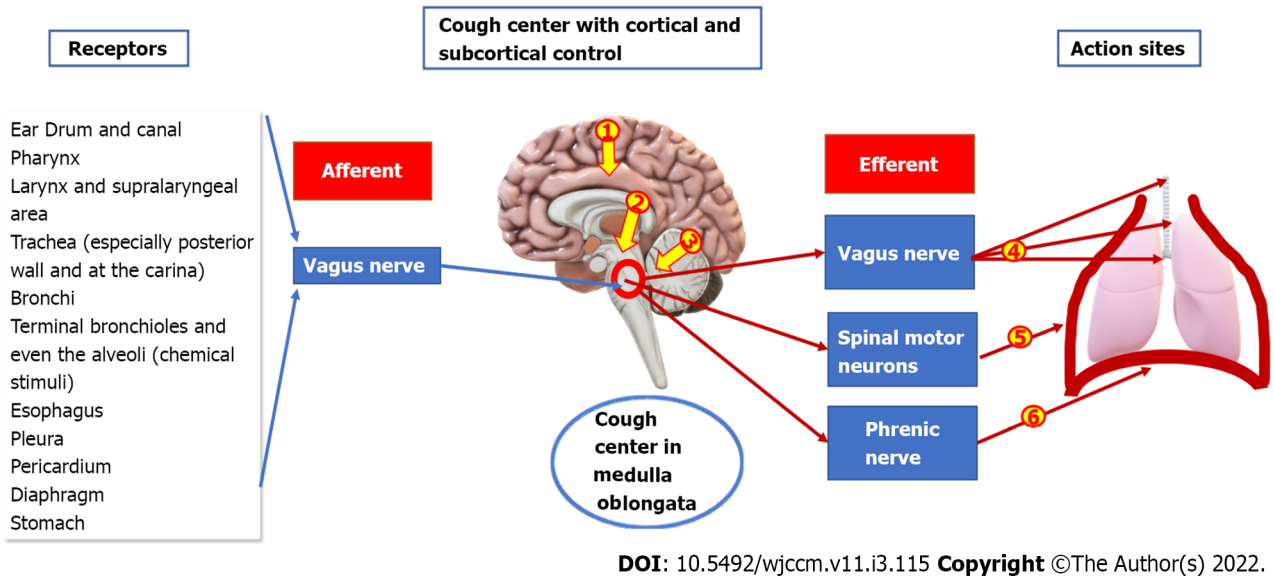

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Figure 1 Cough reflex. The cough center lies in the medulla oblongata in the brainstem. Cough receptors project through the vagus nerve to relay neurons in the solitary nucleus, which project to other parts of the respiratory network, especially the pre-Bötzinger complex. Higher brain centers (cerebral cortex[1]) provide voluntary control over cough, *e.g.*, cough inhibition. However, voluntary coughing does not seem to activate medullary systems. Subcortical centers[2] receive signals from other receptors and other emotional stimuli acting through the hypothalamus. Cerebellum[3] also has control over the cough center. The cough center starts the cough by signaling to the effector organs through the vagus nerve to the larynx, trachea, and bronchi[4], spinal motor neurons[5] to the expiratory muscles, and the phrenic nerve[6] to the diaphragm.

NEUROLOGICAL CONDITIONS ASSOCIATED WITH INCREASED COUGH REFLEX SENSITIVITY

Various neurological diseases could associate with increased cough reflex sensitivity, including cerebral and cerebellar disorders, neuromyelitis optica spectrum disorder (NMOSD), and vagal neuropathy (Table 1).

Cerebral disorders

The urge-to-cough (UTC) is a cognitive sensation needed to initiate and inhibit the reflexive cough stimuli lower than what is usually required to evoke a motor cough. Cough is mediated by the cerebral cortical or subcortical regions and activates multiple brain regions such as the insula, anterior midcingulate cortex, primary sensory cortex, orbitofrontal cortex, supplementary motor area, and cerebellum [9]. Cough, without an apparent medical etiology, is refractory to medical management, underlying a possible psychiatric or psychological basis was previously called psychogenic, habit, or tic cough.

Nowadays, the term "psychogenic" is replaced by "somatic" cough, and the term "habit" was replaced by "tic" cough, according to the Diagnostic and Statistical Manual of Mental Disorders, fifth (DSM-5) edition[10]. The exact prevalence of somatic cough syndrome is not well known due to scarcity and discrepancies in studies. However, it affects about 3% to 10% of children suffering from a chronic cough with unknown causes and about 3.02% of Chinese in-patients with chronic cough[11].

The differentiation between somatic and non-somatic chronic cough is occasionally challenging because patients with chronic cough are more prone to psychomorbidities such as anxiety and depression, which can trigger a chronic cough. Diagnosis of somatic cough syndrome should only be made if the patient meets the DSM-5 criteria, independent of the presence or absence of the nocturnal cough or a cough with a barking/honking quality. Some categories of patients with somatic cough disorders (as children) may benefit from non-pharmacological trials of hypnosis or suggestion therapy or combinations of reassurance, counseling, or referral to a psychologist and/or psychiatrist[12]. Tic cough is a form of vocal or phonic tics characterized by sudden, brief, intermittent, involuntary, or semi-voluntary cough. It may be associated with other motor or vocal tics such as throat clearing, sniffing, grunting, squeaking, screaming, barking, blowing, and sucking sounds[13]. To diagnose the cough as a tic, we depend on core tic criteria such as suppressibility, distractibility, suggestibility, variability, presence of a premonitory sensation, and whether the cough is single or a part of many tics[14]. Tourette's syndrome is a well-described neuropsychiatric disorder characterized by involuntary motor and phonics tics such as coughing, grunting, and wheezing. These phonic tics can be misdiagnosed as respiratory tract disorders such as asthma and upper and lower respiratory system infections. A careful history and thorough neurologic assessment are needed to reach a proper diagnosis. Behavior therapy, psychotherapy, deep brain stimulation, botulinum (Botox) injections, antiepileptics, and antidepressants are possible therapeutic options[15]. When the chronic cough is associated with cerebral manifestations such as truncal ataxia, nystagmus, or incoordination, a central cause in the cough center or higher controlling area should be suspected. Primary central reasons for chronic cough are scarce. A cough may be the initial symptom in patients with Chiari I malformations due to lesions in the dorsal medullary region of the brainstem. A space-occupying brainstem lesion involving the cough center or compressing on the efferent fibers can be a rare cause of chronic cough[16].

NMOSD

NMOSD is a rare autoimmune disease of the central nervous system with inflammation of the long segments of the spinal cord inflammation (myelitis) and optic nerve (severe optic neuritis) with attacks of intractable vomiting and hiccoughs due to autoimmune-mediated lesion affecting the postrema area and medullary floor of the fourth ventricle[17]. An uncontrollable cough may be an added key manifestation aiding the diagnosis of NMOSD, as described in many case reports. The cough is caused by autonomic dysregulation secondary to loss of parasympathetic innervation, which originates predominantly in the nucleus ambiguous of the medulla oblongata[18].

Cerebellar disorders

The neurons in the ventrolateral medulla that create cough and respiratory patterns interact with neural networks in the cerebellum-rostral interposed nucleus, rostral fastigial nucleus, and infra-cerebellar nucleus. The deep cerebellar nuclei are engaged in neural activities necessary for breathing and coughing. For this reason, a dramatic reduction in the cough frequency is observed after cerebellectomy or lesion of the interposed nucleus[19]. In neurodegenerative disorders associated with cerebellar degeneration, there is a reduction in the frequency of coughing episodes that coincides with cerebellar atrophy. However, in a rare type of autosomal dominant cerebellar ataxia (Spinocerebellar ataxia type 5), episodes of spasmodic cough begin 10 to 30 years earlier than the onset of ataxia. It could also be associated with spasmodic dysphonia and tremor. A study from Portugal showed that the prevalence of spasmodic cough is about 2.7% in all the families with documented autosomal dominant cerebellar ataxia. Both spasmodic cough and dysphonia can be caused by laryngeal hyperreactivity and vagal dysfunction. These cough bursts could be considered reliable markers for familial neurodegenerative disease if a previously diagnosed case exists in the family[20].

Vagal neuropathy

The prevalence of chronic cough in vagal neuropathy differs according to the underlying pathology. It is prevalent with laryngeal disorders such as laryngeal sensory neuropathy, postviral vagal neuropathy, and irritable larynx. On the other hand, it is rare with hereditary sensory neuropathy and Vitamin B_{12} deficiency[21]. Cough reflex hypersensitivity manifests by coughing spells, frequently triggered by low threshold stimuli which the patient faces during his usual daily activities such as exposure to a changing temperature, aerosols, perfumes, odors, or during talking or laughing. Cough reflex hypersensitivity is observed in all respiratory diseases (either acute or chronic) when the cough is a predominant feature. At the same time, neuroinflammation is one of the important underlying reasons for cough reflex hypersensitivity[22]. Cranial nerves, including the vagus nerve, can be affected by neuropathic inflammatory processes. The vagus nerve extensively innervates the respiratory and digestive tracts. Vagus nerve dysfunction can trigger cough[23].

Chronic neuropathy of the laryngopharyngeal nerve, a branch of the vagus nerve, presents with symptoms of laryngeal irritation such as chronic cough, stridor, throat irritation, dysphonia, and foreign body sensation in the throat. There is increased cough reflex sensitization with abnormal neuropathic responses to the receptor stimuli in patients suffering from laryngeal neuropathy. Laryngopharyngeal neuropathy can result in changes in the afferent branches of the laryngeal and digestive reflex arch. Consequently, various stimuli like acids can trigger the symptoms. This laryngopharyngeal neuropathy may be associated with paradoxical vocal fold movement as a part of an irritable larynx syndrome where afferent reflex hypersensitivity is a common mechanism[24]. A vagal nerve neuropathy can also impair other motor branches of the vagus nerve, causing paresis or even paralysis of the vocal folds, paradoxical vocal fold movement, or other sensory branches inducing chronic cough and other symptoms such as throat tickling sensation, sore throat, laryngeal paraesthesia, and laryngospasm. These symptoms may be exacerbated and provoked by talking, laughter, irritating inhalants, and laryngeal palpation[25].

Vagus nerve dysfunction can follow viral infections, irritant exposure, or complicated chronic conditions such as asthma. In asthma, elevated substance P and neurokinin A levels in the induced sputum samples reflect airway neuronal activation. Furthermore, neuropeptide calcitonin-gene-related peptide (NCRP) levels in bronchoalveolar lavage from children with chronic cough are positively correlated with capsaicin cough reflex sensitivity. There is an increased expression of NCRP in the nerves supplying the airways in patients with chronic cough[26]. In conditions with intractable coughs, such as idiopathic pulmonary fibrosis, there are high levels of the nerve growth factor in the patients' airways which has significant neuroinflammatory consequences and is one of the factors responsible for cough chronicity[27]. Vitamin B12 deficiency can cause sensory neuropathy resulting in pharyngeal and laryngeal dysfunction, triggering a chronic cough. Vitamin B12 supplementation can improve the histamine threshold and significantly increase the cough threshold in patients with chronic cough due to vitamin B12 deficiency but has no significant effect on subjects without deficiency[28]. Vitamin B12 deficiency-related cough should be in mind in patients treated with proton pump inhibitors or cytotoxic medications.

Behavioral therapy and medical management are needed to treat the hypersensitive cough reflex. Practicing respiratory retraining and learning how to do cough suppression strategies and techniques could help the patients cut the vicious circle of cough by loop suppression of the reflex. A superior laryngeal nerve (SLN) block is another method to help relieve chronic cough due to hypersensitive cough reflex. SLN block can be done as an outpatient service, where a combination of triamcinolone acetonide, lidocaine, and epinephrine is injected into the SLN internal branch at the level of the thyroid membrane. If injection of both sides is needed, we should do one side at a time[29]. Gabapentin, a well-known antiepileptic drug, showed efficacy in controlling epilepsy and various painful conditions such as pruritus, diabetic neuropathy, fibromyalgia syndrome, hiccups, hot flashes, neuropathic pain, and restless leg syndrome. It was also successful in treating some cases of chronic refractory cough. It works by modulating the release of excitatory neurotransmitters, which act by interacting with gamma-aminobutyric acid (GABA) receptors or N-methyl-D-aspartate receptors. Gabapentin is a valuable and safe drug in treating sensory neuropathic cough. Successful control of the cough by Gabapentin can help to confirm the diagnosis of sensory neuropathic cough. Tricyclic antidepressants, amitriptyline, and desipramine can also be used to treat this type of cough, but they are not as safe as Gabapentin, especially in old age[30]. Considering chronic cough as a neuropathic disorder, just like chronic neuropathic pain, will significantly change the potential strategies for diagnosing and managing chronic cough[31].

NEUROLOGICAL CONDITIONS ASSOCIATED WITH DIMINISHED COUGH REFLEX SENSITIVITY

Being a reflex predominantly involves the brainstem and is modulated by the cerebral cortex; cough can be diminished in several neurological disorders affecting the peripheral and central nervous systems. Diminishing cough reflex (dystussia) is associated with a high risk of developing pneumonia and increased morbidity and mortality rates in these diseases (Table 2).

Brain hypoxia and cerebrovascular events

The central nervous system (CNS) is significantly affected by hypoxia, which can depress cough through different mechanisms and decrease the sensitivity of the peripheral cough receptors and the rostral and caudal parts of the solitary nucleus. This nucleus is the recipient of all visceral afferents and an essential part of the regulatory centers of internal homeostasis through its multiple projections with cardiorespiratory and gastrointestinal regulatory centers[32]. The depressive effect of the hypoxia on the solitary nucleus is mediated by the GABA–mediated pathway. GABA is the chief inhibitory neurotransmitter and can down-regulate the cough reflex sensitivity. Therefore, Baclofen, a GABA agonist, can decrease the cough sensitivity to capsaicin in healthy individuals[33]. In addition, hypoxia can increase CNS levels of endogenous opioids, thus reducing the cough sensitivity by inhibiting the central

Table 2 Neurological conditions associated with diminished cough reflex sensitivity

Category	
Cerebral disorders	Brain hypoxia
	Cerebrovascular events
	Dementia
	Parkinson's disease
	Drugs: *e.g.*, antipsychotic drugs, anaesthetics
Amyotrophic lateral sclerosis and multiple sclerosis	
Neuromuscular diseases: *e.g.*, myasthenia gravis	
Peripheral neuropathy	Hereditary sensory autonomic neuropathies
	Phrenic nerve palsy or injury
	Diabetic autonomic neuropathy
	Vitamin B12 and folate deficiency

component of the cough. Hypoxia can occur in many cardiovascular diseases. The hypoxia-related impairment of the cough increases the morbidity and mortality rates in these diseases[34]. Cough reflex can be assessed in a comatose patient as a part of the Brainstem Responses Assessment Sedation Score in the intensive care unit by observing the patient's response to a tracheal suctioning. It is considered positive if any contraction of abdominal muscles is observed[35].

Cortex has control over the cough. The ability to voluntarily produce and suppress a cough is an example of the cortical control of the cough. Reduced strength of the voluntary cough may increase the risk of aspiration and other pulmonary consequences due to inadequate clearing of the aspirated material from the airway, as seen in patients with brainstem or cerebral stroke associated with an abnormal laryngeal cough reflex[36]. Many patients with cerebral hemispheric stroke showed a temporary or long-lasting malfunction of the laryngeal cough reflex (Known as "brainstem shock"). This shock is characterized by a generalized transient or permanent neurological malfunction of one or more vital neurological functions, including the respiratory drive, reticular activating system, or the laryngeal cough reflex.

Consequently, many patients with significant or minor hemispheric strokes may develop impaired consciousness and need intubation due to reduced respiratory drive. Addington *et al*[37] showed the importance of the stroke location in determining the effect of stroke on the laryngeal cough reflex and consequently on the pneumonia risk. They showed that the brainstem and cerebral hemispheric infarcts are more liable to affect the laryngeal cough reflex than basal ganglionic or cerebellar infarcts[37]. Daniels *et al*[38] showed that 67% of their patients with stroke did not show cough response, and 38% had suffered from aspiration[38]. Therefore, adding cough sensitivity testing to the clinical evaluation of the swallowing function will significantly reduce the aspiration pneumonia risk in patients with cerebral or brainstem stroke[7]. It also helps in monitoring the recovery from stroke and evaluating the postsurgical recovery of the laryngeal cough reflex after extubation and following general anesthesia [39].

Patients with Lewy body disease-related dementia have decreased cough reflex sensitivity and central respiratory chemosensitivity, with decreased insula activation associated with UTC[9]. Patients with Parkinson's disease also have reduced intensity of voluntary and reflex cough efforts with a slightly higher cough threshold. Fontana *et al*[39] found that a motor rather than a sensory component of the cough reflex is primarily involved, especially in the early stages, primarily due to impairment in the central activation of motor units and reduced neural drive to expiratory muscles. The impaired central activation reflects the presence of bradykinesia which is one of the critical functional disorders in these patients[36]. Parkinsonism is associated with decreased Dopamine and other neurotransmitters production in substantia nigra, impairing substance P production in vagal sensory nerve C-fibers in the cervical ganglia. The low level of substance P weakens the swallowing reflex and suppresses the cough reflex causing frequent aspiration[40]. About 20% of deaths in patients with Parkinsonism were related to pneumonia, probably because of the impaired cough reflex and upper airway muscle dysfunction [41]. In the same way, multiple sclerosis, with its characteristic disseminated demyelination patches in both the brain and spinal cord, can affect the voluntary cough efficiency and respiratory muscle power due to bulbar dysfunction and corticospinal tract damage in the spinal cord. The degree of impairment of cough reflex has an inverse correlation with the patients' degree of disability[42].

Motor neuron diseases

Motor neuron disease is a chronic degenerative neurological disorder affecting the corticospinal tracts,

motor nuclei in the brainstem, and the anterior horn cells of the spinal cord. It reduces the capacity of efficient cough. There is a hyperactive cough reflex in its early stages due to inflammatory mediators such as bradykinin and prostaglandins. As the disease progresses, there is continuous damage-causing cough desensitization. Various combinations of upper and lower motor neuron dysfunction may increase the need to cough but, unfortunately, impair the efficiency of both the voluntary and reflex types of coughs[43]. Amyotrophic lateral sclerosis is characterized by upper (UMN) and lower motor neuron (LMN) degeneration which negatively impacts the ability of respiratory and laryngeal musculature to work in harmony during the cough phases. The rigidity due to UMN degeneration and weakness due to LMN degeneration led to abnormal cough flow and impaired airway clearance abilities, causing different pulmonary sequelae, such as poor secretion management, recurrent pneumonia, and even respiratory failure[44]. Voluntary cough testing detects the presence of dysphagia and impaired airway defense physiologic capacity and secretion management. Constant assessment of voluntary cough function provides rapid detection of respiratory deterioration, permitting appropriate implementation of cough assist, non-invasive ventilation, and respiratory training before significant function degradation[45].

Neuromuscular diseases

Neuromuscular diseases are associated with increasing breathing disorders, including swallowing dysfunction, cough impairment, and frequent choking. In myasthenia gravis, cranial nerves impairment and bulbar weakness could be the initial symptoms causing frequent aspiration and, consequently, increasing the coughing frequency. However, if the patient develops a respiratory failure, the associated hypoxia causes peripheral and central impairment of the cough reflex sensitivity[46]. Phrenic nerve palsy or injury is associated with decreased cough reflex[47].

Peripheral neuropathy

Since cough is a defensive reflex, it could be affected by diseases targeting the peripheral nerves. Consequently, vagotomy or anesthesia-induced vagal block abolishes cough[48]. Hereditary Sensory Autonomic Neuropathies (HSAN) are rare hereditary peripheral neuropathies characterized by the loss of large myelinated and unmyelinated fibers resulting in decreased pain sensation and its associated consequences. Congenital insensitivity to pain with anhidrosis (CIPA) is HSAN type-IV; it occurs due to a mutation in the gene encoding for the neurotrophic tyrosine kinase receptor type I, called the *NTRK1* gene[49]. Both pain and cough can be evoked experimentally by stimulating nociceptive C-fibers and faster-conducting A-δ-fibers. Consequently, CIPA can impair both pain and cough. Few cases reports described this association[50,51].

Diabetes-related autonomic neuropathy is one of the most typical complications of diabetes mellitus (DM). Meanwhile, the vagus nerve is one of the first nerves damaged in DM. Different studies showed a significant increase in the cough threshold with cough reflex impairment. Ciljakova *et al*[52] found a robust negative correlation between cough reflex sensitivity and heart rate variability as an indicator of diabetic autonomic neuropathy[52]. Down-regulation of the cough reflex may start very early in the pathogenesis of diabetes. Varechova *et al*[53] found decreased cough reflex sensitivity in children with Type-I DM with subclinical autonomic neuropathy. Testing those children for reduced cough reflex could reflect the presence of autonomic dysfunction and its impact on respiratory and general health [53]. Cough reflex sensitivity could also decrease with aging, during sleep, cranial nerve conduction abnormalities due to vitamin B12 and folate deficiency, and inhibition of dopamine receptors by antipsychotic drugs[40].

HOW CAN COUGH HELP TO DIAGNOSE NEUROLOGIC DISORDERS?

When a chronic cough is present, the underlying lesion should be investigated.

Arnold's nerve ear-cough reflex

In Arnold's nerve ear-cough reflex, the cough is triggered by mechanical stimulation of the external auditory meatus through the auricular branch of the vagus nerve (Arnold's nerve), which supplies the external auditory canal, middle ear, and auditory tube. The test is done using a cotton swab on a stick to stimulate the ear by placing the swab 3 to 5 mm into the external auditory canal and rotating for 2 to 3 s. We consider the test positive if the patient coughs within 10 s. The test should be performed on both sides, as many persons may only have one affected side. The test is positive in 2% of healthy children and adults, 3% of children, and 25% of adults with chronic cough. A positive reflex is more common in women than men and is unilateral in over 90% of patients[54].

Interestingly, hair within the ear canal can stimulate Arnold's nerve and trigger the urge to cough (Oto-tricho-tussia). Such patients can be easily treated by removing the hair[55]. This effect can be applied to any foreign body or earwax impaction in the auditory canal. Consequently, examining the external auditory canal should be a routine in patients with chronic cough, especially in old age[56]. The high prevalence of positive Arnold's nerve reflex in patients with chronic cough suggests that chronic

cough is a neuropathic condition due to a disorder or alteration in the vagus (vagal hypersensitivity) that could be secondary to sensory nerve damage caused by the inflammatory, infective, or allergic factors. It is usually accompanied by other neuropathic features such as throat irritation (laryngeal paraesthesia). Cough is triggered upon exposure to non-tussive triggers such as cold air and eating (allotussia or UTC). The low prevalence of positive reflex in children with chronic cough (3%) compared to the adults (25%) indicates that the hypersensitivity of this reflex may be acquired, possibly by a viral infection[57]. A positive Arnold's nerve reflex can be reversed after successful therapy of chronic cough. However, a positive Arnold's nerve reflex is not a valid predictor of the cause of chronic cough but can trigger the need to investigate it[58].

Holmes-Adie syndrome

Holmes-Adie syndrome is another rare cause of tendon areflexia, unilateral or bilateral tonic pupils with slow reaction to near direct light, and chronic cough; due to autonomic dysfunction affecting some cranial nerves, including the vagus nerve. Autonomic dysfunction is a frequent finding for this condition; attributed to lesions in both afferent and efferent sympathetic and parasympathetic neurons. Airways reflux secondary to vagal dysfunction is a possible etiology of cough in these patients. The patients present with anisocoria, abnormal deep tendon reflexes, patchy hyperhidrosis or anhidrosis, and chronic cough[59]. Many patients with sensory neuropathic cough were relieved by neuralgia-neuromodulator drugs, such as amitriptyline, desipramine, Gabapentin, pregabalin, oxcarbazepine, and others, when other potential causes of chronic cough have been ruled out. These medications may help reduce or abolish cough by diminishing the nerve-ending "misfires" caused by sensory neuropathic cough[60].

Cough syncope

Cough syncope is a temporary impairment or loss of consciousness with facial congestion and cyanosis; it typically occurs within seconds of a coughing paroxysm, followed by a rapid recovery. Cough syncope originally can mimic epilepsy. It was previously considered a form of epilepsy "known as laryngeal epilepsy" because of the associated jerking movements. However, many studies showed regular brain electrical activity during the episodes. It typically occurs in middle-aged and older, overweight, or muscularly built male smokers with a history of chronic obstructive lung disease. These persons are more prone to create a very high intrathoracic pressure associated with cough-induced syncope and fainting[61]. As it is mainly an adult disease, cough syncope was rarely reported in children, particularly under ten years[62]. The exact mechanism of cough syncope is debatable. Cough markedly elevates the intrathoracic pressures, diminishes the cardiac output, and decreases the systemic blood pressure and cerebral perfusion. At the same time, cerebrospinal fluid (CSF) pressure increases causing reduced brain perfusion; or a cerebral concussion-like effect due to rapid CSF pressure elevation. Another theory suggests that the cough initiates a neurally-mediated reflex vasodepressor-bradycardia. Elimination of cough eliminates the resultant syncopal episodes[63].

The patient may have a fixed upward deviation of the eyes during the syncopal episode, which should not be confused with epilepsy. EEG shows temporary slowing during the attack but no seizure discharges. It is always accompanied by a coughing paroxysm. During the attack, the face becomes plethoric rather than cyanotic, and the entire episode lasts less than a minute. An aura never precedes it and is very rarely followed by post-ictal confusion/headache. Cough syncope frequently occurs at night while prone, whereas epilepsy can develop in any position[64]. Cough syncope is associated with a high incidence of pulmonary, cardiac, and neurologic disorders. Numerous CNS disorders were reported to be associated with cough syncope, including cerebral tumors (meningioma, glioblastoma), herniation of cerebellar tonsils (Type 1 Arnold-Chiari malformation), hydrocephalus, carotid and vertebral arterial occlusive disease, basilar invagination, autosomal dominant hereditary sensory neuropathy, and medullary infarction[65].

Cough headache

Cough-triggered headaches are uncommon, with a lifetime prevalence of 1%. Headache can be triggered by a rapid increase in the intra-abdominal, intra-thoracic, and intracranial pressure, caused by coughing, sneezing or straining in patients with low pain threshold[66]. It is either primary or symptomatic. Primary cough headache (previously known as benign cough headache or Valsalva maneuver headache) is currently defined as a headache with sudden onset, occurring only in association with coughing, straining, and/or Valsalva maneuver. It lasts from one second to 30 min and is unrelated to other disorders[67]. It is more frequent in males over 40 years, and usually bilateral, but sometimes unilateral. Pain is of moderate-to-severe intensity and is usually located in the fronto-temporal regions, but sometimes presents with different patterns such as toothache. The pain can be triggered by Valsalva maneuvers but never by physical exercise. Nausea, vomiting, photo- and phonophobia are uncommon[68].

Underlying disorders can be detected in 40% of cases with symptomatic cough headaches. These lesions may involve but are not limited to Chiari type I malformation, obstructive hydrocephalus, posterior fossa structural lesions (as arachnoid cysts, dermoid tumors, meningiomas, or Os

odontoideum), spontaneous low CSF pressure or leak, subdural hematoma, multiple brain metastases, acute sphenoid sinusitis, pneumocephalus, pneumococcal meningitis, or non-ruptured cerebral aneurysm[69]. Symptoms are more common than those observed with the primary type, depending on the underlying abnormality. The headache is increasing in intensity with variable durations and locations. The pain may be pressing, explosive, bursting, stabbing, dull, electrical, lancinating, or having a mixed nature. Headache duration ranges from seconds to several weeks[65]. Headache can be triggered by a cough and other factors such as laughing, exertion, weightlifting, defecation, or rapid body or head postural changes. Posterior fossa symptoms are common, such as dizziness, unsteadiness, facial and upper limb numbness, vertigo, and syncope. The mechanism of headache is due to raised intracranial pressure, evidenced by the disappearance of the headache after surgical correction of the lesion[70].

Opioids-associated cough

Opioids are well known to have a central antitussive action. However, some opioids such as Alfentanil, Fentanyl, and Sufentanil can elicit a brief tussive effect in about 50% of the patients (especially smokers) within a few seconds from the rapid bolus intravenous injection. This tussive effect is due to the chemical stimulation of opioid receptors in the smooth muscles in the trachea, bronchi, and bronchioles. This pulmonary chemoreflex is unlikely to be mediated by the vagus nerve, as it is not affected by atropine pretreatment. Instead, pretreatment with inhaled β-2 adrenergic agonists considerably decreases the rate of cough related to the intravenous opioid injection. This opioid-associated cough is usually self-limited. It is also related to circulation time and could serve as a clinical landmark for vein-to-brain time or cardiac output[71].

Cough-anal reflex

The anal wink in response to cough or sniff is a significant clinical sign during a neurological examination. It could be elicited by asking the patient to voluntarily cough or sniff while observing the anus. This reflex is not affected by transection of the spinal cord while being lost in cauda equina lesions. It is easier to be done and more convenient to the patient than the classic anal reflex. It is a promising tool and is better to be included in the neurological examination[72].

OTHER RESPIRATORY SYMPTOMS THAT COULD HAVE NEUROLOGICAL PATHOLOGY

Many other respiratory symptoms and signs could have underlying neuropathologies. Intractable sneezing and hiccup could be seen in patients with NMOSD[73]. However, a diminished sneezing reflex or difficulty initiating sneezing or the urge to sneeze is an uncommon neurological symptom. A runny nose and hypo or hyper-reflexive rhinopathy could indicate autonomic nervous system dysfunction [74]. Nasal discharge may be observed in Parkinson's disease, dementia, and Alzheimer's disease or arise from their treatment[75]. CSF rhinorrhea is observed in head trauma and can be easily distinguished by a simple glucose dipstick test[76]. Throat clearing, dysphonia, and vocal fatigue can be observed in many patients with postviral vagal neuropathy[77]. However, a detailed discussion of these symptoms is out of the scope of this review.

TREATMENT OF NEUROLOGICAL DISEASE-RELATED COUGH

Treatment of cough secondary to neurogenic disorder is mainly directed to treat the cause. A suggested guideline for managing chronic neuropathic cough is demonstrated in Figure 2. Different modalities could be used to treat these coughs after trying to treat the original neurogenic disorder. Speech and language therapy, behavior modification, biofeedback, self-hypnosis, bed-sheet technique, and differential reinforcement can help treat somatic cough[21]. We can also try combined codeine and guaifenesin or empiric therapy with Gabapentin, Pregabalin, Nortriptyline, or Amitriptyline[78]. Botulinum toxin injection into the thyroarytenoid muscles or vocal cords may help to relieve chronic cough secondary to a neuropathic disorder[79]. Referral to a Specialist cough clinic could be an excellent choice to reach a definitive treatment for chronic cough not responding to the previous management. Enrolment in ongoing clinical trials could also be a valid option. Transcutaneous electrical nerve stimulation is a relatively new electroanalgesia method that helps relieve neuropathic pain disorders, including refractory chronic neuropathic cough, which is physiologically like other neuropathic pain conditions. Michalowski *et al*[80] studied the tolerability and feasibility of using Transcutaneous electrical nerve stimulation to treat neuropathic cough[80]. Other new modalities and novel therapeutic agents are under trial, especially those working on the brainstem and cerebral cortex.

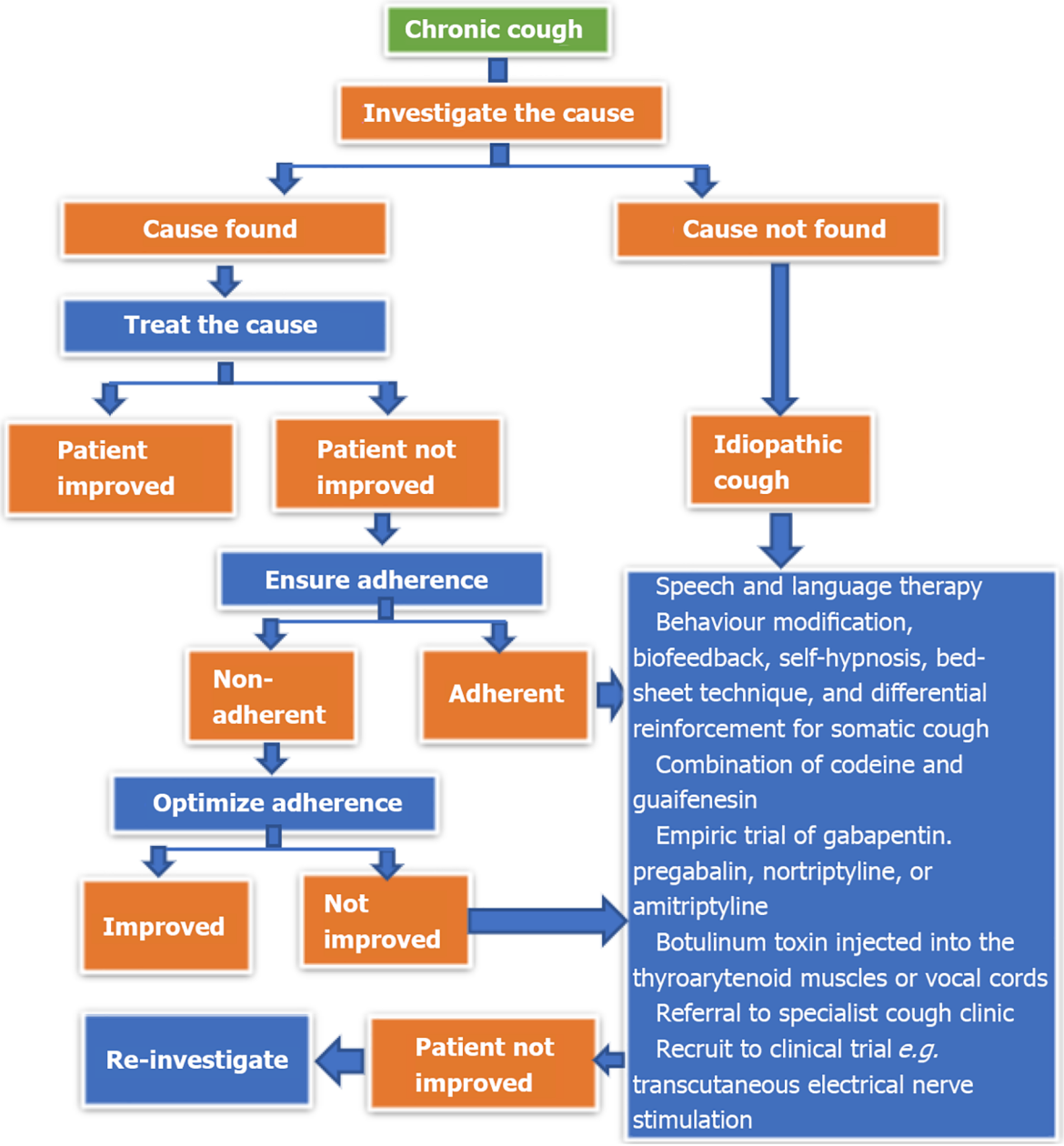

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Figure 2 Proposed guidelines for the treatment of chronic cough.

CONCLUSION

A cough is a crucial neurological sign, the same as a critical respiratory sign. Cough reflex sensitivity could be increased or decreased in many neurological disorders. Cough reflex testing is quick, easy, and cheap tests can be performed during the cranial nerve examination.

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Country/Territory of origin: Bahrain

ORCID number: Mohammed Al-Biltagi 0000-0002-7761-9536; Adel Salah Bediwy 0000-0002-0281-0010; Nermin Kamal Saeed 0000-0001-7875-8207.

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MINIREVIEWS

Presentation and outcome of myocardial infarction with non-obstructive coronary arteries in coronavirus disease 2019

Kevin John, Amos Lal, Nitish Sharma, Amr ElMeligy, Ajay K Mishra

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Kevin John, Department of Critical Care, Believers Church Medical College Hospital, Thiruvalla 689103, Kerala, India

Amos Lal, Division of Pulmonary & Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Nitish Sharma, Division of Cardiology, Saint Vincent Hospital, Worcester, MA 01608, United States

Amr ElMeligy, Division of Interventional Cardiology, Saint Vincent Hospital, Worcester, MA 01608, United States

Ajay K Mishra, Department of Cardiovascular Medicine, Saint Vincent Hospital, Worcester, MA 01608, United States

Corresponding author: Ajay K Mishra, FACP, MBBS, MD, Assistant Professor, Postdoctoral Fellow, Department of Cardiovascular Medicine, Saint Vincent Hospital, 123 Summer Street, Worcester, MA 01608, United States. ajay.mishra@stvincenthospital.com

Abstract

Among the cardiac complications of coronavirus disease 2019 (COVID-19), one increasingly reported in the literature is myocardial infarction with non-obstructive coronaries (MINOCA). We reviewed all reported cases of MINOCA in COVID-19 patients to summarize its clinical features, evaluation, and treatment. We performed a literature search in Pubmed using the search terms 'COVID-19' and 'MINOCA' or 'non-obstructive coronaries'. Among the reported cases, the mean age was 61.5 years (SD ± 13.4), and 50% were men. Chest pain was the presenting symptom in five patients (62.5%), and hypertension was the most common comorbidity (62.5%). ST-elevation was seen in most patients (87.5%), and the overall mortality rate was 37.5%. MINOCA in COVID-19 is an entity with a broad differential diagnosis. Therefore, a uniform algorithm is needed in its evaluation to ensure timely diagnosis and management.

Key Words: COVID-19; Myocardial infarction with non-obstructive coronary arteries; Outcome

Core Tip: Myocardial infarction with non-obstructive coronary arteries (MINOCA) may be more commonly seen in patients with coronavirus disease 2019 (COVID-19). To ensure that cases of MINOCA are identified and managed appropriately, a well-defined, algorithmic approach should be taken while evaluating COVID-19 patients with evidence of myocardial injury. This review summarizes the clinical characteristics and outcomes of all COVID-19 patients with MINOCA reported to date.

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INTRODUCTION

Myocardial infarction with non-obstructive coronaries (MINOCA) is defined as a rise or fall of cardiac troponin, with at least one value above the 99th percentile of the upper reference limit, corroborative clinical evidence of infarction (classic symptoms, electrocardiogram changes, or new wall motion abnormality), non-obstructive coronary arteries on angiography (< 50% obstruction), and lack of an alternative diagnosis[1]. MINOCA is seen in 5%-6% of patients with acute myocardial infarction (AMI)[2]. However, this number may be as high as 15% in certain subgroups[2]. Compared to patients with AMI due to obstructive coronary artery disease (CAD), patients with MINOCA are younger, consist of more women, and have a lesser prevalence of traditional risk factors such as dyslipidemia, diabetes mellitus, hypertension, tobacco use, and family history of AMI[1].

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to more than 4,250,000 deaths worldwide. Although primarily a respiratory illness, it is becoming increasingly clear that COVID-19 is a multi-system disease. How COVID-19 affects the cardiac system has been well documented. However, as more cases are reported, uncommon presentations and complications of COVID-19 are surfacing. Although there have been many reports of MINOCA in COVID-19 patients, a unified approach to evaluate such patients is lacking. In this paper, we review cases of MINOCA reported in patients with COVID-19 and provide a summary of its clinical features, evaluation, and treatment.

METHODS

In this review, we included articles on COVID-19 and MINOCA published in PubMed until January 2022. We used the search terms 'COVID-19' and 'MINOCA' or 'non-obstructive coronaries'. Case reports, case series, retrospective, and prospective observational studies on adult patients with COVID-19 were eligible to be included. We excluded opinions, recommendations, and reviews that did not have clinical details of patients. Patients whose initial diagnosis of MINOCA was modified after further evaluation were also excluded. Studies in languages other than English were translated using Google Translate. Two independent clinicians were involved in the screening of the articles.

RESULTS

We found five cases and one case series of three patients with MINOCA and COVID-19[3-8] (Table 1). We also found five observational studies of MINOCA in COVID-19 patients, which are discussed seperately[9-13] (Table 2). Among the reported cases, the mean age of patients was 61.5 years (SD ± 13.4), and 50% were men.

Demographic details and presentations

Chest pain was the presenting symptom in five patients (62.5%), two patients (25%) had dyspnea without chest pain, and one patient (12.5%) was found unresponsive at the time of presentation. Hypertension was the most common comorbidity and was present in 62.5% of the patients. Other comorbidities included diabetes mellitus, chronic obstructive pulmonary disease, non-ischemic heart failure with reduced ejection fraction, past ST-elevation myocardial infarction (STEMI), hypercholesterolemia, and motor-neuron disease.

Table 1 Case reports of myocardial infarction with non-obstructive coronary arteries in coronavirus disease 2019

Sl. No	Ref.	Age in yr	Sex	Presenting complaint	Comorbidities	Chest imaging	ECG	Cardiac troponins	Echocardiogram	Angiogram	Other investigations	Management	Outcome
1	[3]	47	M	Shortness of breath for 6 d, angina on day 2 of admittion	Hypertension	CT thorax: Diffuse bilateral infiltrates, ground glass opacities, crazy paving with thickened interlobular septa, and consolidation in lower lobes	Inferior STEMI	0.012 ng/mL (Ref range: < 0.0262 ng/mL)	Not reported	Emergency coronary angiography showed 30%-40% stenosis in the midportion of the left anterior descending artery. In addition to this, the left main coronary artery, left circumflex artery and right coronary artery were normal. ST segment elevation regressed in the ECG of the patient, who had no more ischemic cardiac symptoms after the intervention	CTPA did not reveal any evidence of pulmonary embolism. Cardiogoniometry (a non-invasive medical tool worked with spatiotemporal vectocardiographic advancement), was performed after 24 h of the pain, it revealed septal inferior myocardial ischemia	300 mg po acetylsalicylic acid, 180 mg po ticagrelor, and 4000 IU IV heparin	Discharged on the eleventh day of his hospitalization in a healthy state
2	[4]	48	F	Pain in her chest and left shoulder for 1 day	none	none	Inverted T-waves in II, III, aVF, V4, V5, and V6	Upward of 25000 pg/mL (Ref range: 0.0–51.4 pg/mL)	Hypokinesis in the apical inferior segment of the left ventricle	CTCA was performed to exclude a coronary origin for the complaints and for the laboratory and ECG abnormalities, which revealed no significant coronary obstruction	CMR showed features of myocardial oedema restricted to the mid-ventricular to apical territory of the right coronary artery (RCA). Based on subendocardial to partially transmural late gadolinium enhancement in the mid-ventricular to apical inferior wall, an acute myocardial infarction was diagnosed. Cardiac positron emission tomography–computed tomography showed evidence of reduced metabolic activity in the area affected by the infarction	Acetylsalicylic acid, prophylactic-dose low-molecular-weight heparin, and statin. Later dual anti-platelet therapy and an angiotensin-converting-enzyme inhibitor was started	Discharged. Follow-up echocardiography 2 d after discharge revealed a normal ejection fraction (58%) despite persistent inferior apical akinesia
3	[5]	86	M	Cough and shortness of breath which progressed		Chest X-ray: bilateral infiltrates at the bases with no	3–4 mm ST-segment elevations in leads V2 and	4.82 ng/mL (Ref range: < 0.10	Ejection fraction of 50%–55%, no significant regional wall motion	No significant coronary artery disease		Admitted to the intensive care unit, requiring mechanical ventilation and	Respiratory status worsened and he required increased oxygen and positive

				to acute hypoxemic respiratory failure requiring intubation		other abnormalities	V3	ng/mL	abnormalities, and no signs of cardiac tamponade			vasopressor support	end-expiratory pressure, renal function worsened, as did lymphopenia and inflammatory biomarker abnormalities. Died on day 8
4	[6]	61	M	Shortness of breath, respiratory failure requiring intubation	Hypertension, diabetes mellitus		2 mm of antero-lateral ST-elevation without reciprocal depression	6283 ng/L (Ref range: < 40 ng/L)	Moderate left ventricular systolic dysfunction	No luminal stenosis or thrombosis, with preserved TIMI 3 flows in all coronary arteries	Left ventriculography: Mild apical hypokinesis	Loading dose of ticagrelor and IV heparin	On day 13, he was anuric and CVVH was started. Continued to worsen and died
5	[6]	59	F	Found minimally responsive on the ground. Intubated by paramedics	Hypertension, COPD	CT thorax: Bilateral lower lung lobe infiltrates and pulmonary oedema with moderate calcification in the mid-left anterior descending artery	ST-segment elevations in V1–V4 and reciprocal ST-depressions in leads II, III, and aVF	2390 ng/L	reduced left ventricular ejection fraction of 40% with antero-apical wall hypokinesis	Moderate diffuse atherosclerotic disease was observed in the left system with no significant luminal obstruction elsewhere		Not specified	Extubated on Day 3. Discharged home subsequently
6	[6]	69	F	acute onset chest tightness and dyspnea	Non-ischemic heart failure with reduced ejection. Implantable cardioverter-defibrillator was placed in 2004. Motor neurone disease, diagnosed 4 yr previously	Chest X-ray: Bilateral infiltrates	Left bundle branch block. On day 3 progressive dynamic concordant ST-elevation in V1–V2 and ST-depression in V3–V5	504 ng/L	Impaired left ventricular function which was similar to baseline	No obstructive atheroma or thrombus		Loading dose dual antiplatelets, therapeutic low molecular weight heparin, high-dose IV diuretics, and IV nitrates	The patient died on Day 7 of admission
7	[7]	51	M	Left sided chest pain, diaphoresis, syncope	Hypertension and hypercholesterolemia	Chest X-ray: Bilateral interstitial prominenceCT chest: perihilar ground glass opacities, thickening of interlobular septa, and minimal bilateral	3.5 mm ST elevation in I and avL, 5 mm isolated ST elevation in lead V2, with deep reciprocal depressions in III, avF and avR	Not reported	Preserved left ventricular ejection fraction (LVEF) of 55% and anteroapical hypokinesis on ventriculography	Patent coronary arteries		Admitted to Cardiac Intensive Care Unit and started on supportive measures. Treated with lopinavir/ritonavir 400 mg/100 mg tablet every 12 h for 4 d and hydroxychloroquine 500 mg every 12 h, then hydroxy-	The patient recovered and was discharged home on day 26 on aspirin, statin and metoprolol

						pleural effusions, interpreted as consistent with congestive heart failure						chloroquine alone 400 mg daily	
8	[8]	71	F	Chest-pain	Hypertension, past STEMI	Chest X-ray: No pulmonary opacities	ST-segment elevation in inferior leads, and ST depression, and inverted T waves in V1-3	Negative	Preserved left ventricular ejection fraction of 50% with inferior and septal hypokinesis	Non-obstructive coronary artery disease		Loading dose of ticagrelor and unfractionated heparin	Discharged

M: Male; F: Female; ECG: electrocardiogram; CT: Computed tomography; STEMI: ST-elevation myocardial infarction; CTPA: Computed tomographic pulmonary angiography; CTCA: Computed tomography coronary angiography; CMR: Cardiac Magnetic Resonance Imaging; TIMI: Thrombolysis in myocardial infarction; CVVH: Continuous veno-venous hemofiltration; COPD: Chronic Obstructive Pulmonary Disease.

Investigations

ST-elevation was seen in most patients (87.5%), while one patient (12.5%) had only T-wave inversion. In addition, a new-onset left bundle branch block was seen in one patient (12.5%)[6]. Three-quarters of all patients had elevated troponin levels. On echocardiography, three patients (37.5%) had reduced ejection fraction, and four (50%) had preserved ejection fraction. One case report did not include echocardiography findings. Non-obstructive coronary arteries were demonstrated by invasive angiography in all patients, except one who underwent computed tomography coronary angiography (CTCA)[4]. Cardiac magnetic resonance imaging (CMR) was performed on one patient. It showed myocardial edema restricted to the mid-ventricular to apical territory of the right coronary artery, and subendocardial-to-partially transmural late gadolinium enhancement in the mid-ventricular to apical inferior wall. These findings were suggestive of acute myocardial infarction[4]. The same patient underwent cardiac positron emission tomography-computed tomography (PET-CT), which showed reduced metabolic activity in the area affected by the infarction. Another patient underwent computed tomographic pulmonary angiography, which ruled out pulmonary embolism, and cardiogoniometry, which revealed septal inferior myocardial ischemia[3].

Treatment and outcome

While most patients were treated with supportive care, antiplatelets, statins, and anticoagulation, one patient received anti-viral therapy (lopinavir/ritonavir) with hydroxychloroquine[7]. The overall mortality rate was 37.5%.

Observational studies reporting outcomes of MINOCA in COVID-19

In the five observational studies included in this review, the incidence of MINOCA among COVID-19 patients with an acute coronary syndrome varied from 5.2% to 54.5%[9-13]. Demographic details were only reported in the study by Stefanini *et al*[9]. The mean age of patients with MINOCA in that study was 69.27 years (SD ± 10.6), and 54.5% were male. Hypertension was the most common comorbidity

Table 2 Studies that reported myocardial infarction with non-obstructive coronary arteries in coronavirus disease 2019

Sl. No	Ref.	Total number of patients with MINOCA (%)	Mean age	Male (%)	Comorbidities (%)	Smoking(%)	Prior MI (%)	LVEF	EKG (%)	Mortality (%)
1	[9]	11/28 (39.3)	69.27 ± 10.6	6 (54.5)	Diabetes mellitus: 1/11 (9.1), Hypertension: 9/11 (91.8), Dyslipidemia: 3/11 (27.3), Chronic kidney disease: 5/11 (45.4)	1/11 (9.1)	1/11 (9.1)	43 ± 12.7	ST elevation: 9/11 (81.81), New onset LBBB: 2/11 (18.2)	5/11 (45.4)
2	[10]	6/11 (54.5)	-	-	-	-	-		-	-
3	[11]	3/9 (33.3)	-	-	-	-	--	Low ejection fraction and RWMA in 2 patients (ECHO not done for third)	ST elevation: 3/3 (100)	2/3 (66)
4	[12]	1/19 (5.2)	-	-	-	-		-	-	-
5	[13]	5/29 (17.24)	-	-	-	-	-	-	-	-

MINOCA: Myocardial infarction with non-obstructive coronary arteries; MI: Myocardial infarction; LVEF: Left ventricular ejection fraction; EKG: Electrocardiogram; LBBB: Left bundle branch block: RWMA: Regional Wall Motion Abnormality: ECHO: Echocardiography.

(91.8%), followed by chronic kidney disease (45.4%), dyslipidemia (27.3%) and diabetes mellitus (9.1%). The proportion of patients with ST-elevation on ECG was between 81.8% and 100%, and the mortality rate ranged from 45.4% to 66%.

DISCUSSION

Gross and Sternberg first described MINOCA in 1939[14]. Later, the term MINC or MINCA (myocardial infarction with normal coronary arteries) was coined, which was modified to MINOCA to be more inclusive. Other words that have been used in the literature to describe this pathology include 'acute coronary syndromes with normal or near-normal coronary arteries' (ACS-NNOCA) and ischemic syndromes with non-obstructive coronaries (INOCA). Strictly speaking, MINCA is a subset of MINOCA, which is a subset of ACS-NNOCA. The subtle differences between these terms have been confusing as these terms are often used interchangeably. Nevertheless, the term MINOCA provides a framework for evaluating such patients and is often used as a 'working diagnosis'. Further evaluation may reveal secondary causes such as myocarditis, Takostubo cardiomyopathy, sepsis, cardiac contusion, spontaneous coronary artery dissection, microvascular disease, coronary artery spasm, or missed obstructive coronary artery disease. If a secondary cause is not found, a diagnosis of 'unclassified MINOCA' is made[1].

The proportion of MINOCA seems to be higher in COVID-19 patients. In the study by Popovic *et al* [10], there was a statistically significant increase in the proportion of MINOCA in COVID-19 patients compared to a historical cohort (54.5% *vs* 1.4%, $P < 0.001$). Due to the heterogeneity in case definitions and evaluation protocols between centers, the actual proportion of MINOCA among COVID-19 patients is difficult to estimate. One can gauge the upper limit of this estimate from the proportion of COVID-19 patients with acute cardiac injury (ACI), which is one of the earliest measures of cardiac involvement reported during the COVID-19 pandemic. ACI, defined as cardiac-troponin elevation with values exceeding the 99th percentile of the upper reference limit, was observed in 8%-62% of COVID-19 patients [15]. Also noteworthy was that any amount of cardiac injury was significantly associated with mortality (adjusted HR 1.75, $P < 0.001$)[16].

Some other characteristics of COVID-19 patients with MINOCA can be extrapolated from the results of a systematic review of 161 patients from 42 studies of COVID-19 patients with ST-elevation[17]. The authors observed that patients with non-obstructive CAD had more diffuse ST-segment elevation (13% *vs* 1%, $P = 0.03$) and diffuse left ventricular wall-motion abnormality (23% *vs* 3%, $P = 0.02$) when compared to those with obstructive CAD[17]. In the same review, the proportion of men in the group with obstructive CAD was higher than in the group with non-obstructive CAD (79% *vs* 57%)[17].

Our literature review found that many patients with COVID-19 and MINOCA received alternative diagnoses such as Takotsubo cardiomyopathy, coronary vasospasm, myocarditis, and coronary vasculitis on further evaluation. This is consistent with the concept that MINOCA is a dynamic diagnosis, and patients who were initially diagnosed with MINOCA may receive a revised diagnosis on

further evaluation. However, some patients were presumed to have myocarditis without objective evidence for the same[18-21]. A diagnosis of MINOCA or MINOCA under evaluation would better suit such patients. It must also be noted that the cases of MINOCA with COVID-19 that were included in this review are cases of 'unclassified MINOCA.'

Specific causes for MINOCA in COVID-19 patients

Myocarditis: Myocarditis is defined as an inflammatory disease of the myocardium diagnosed by histological, immunological, immunohistochemical, and molecular criteria[22]. There have only been a handful of COVID-19 patients with endomyocardial biopsy-proven myocarditis[23,24]. Even in these patients, the SARS-CoV-2 genome could not be isolated from the biopsy sample. Thus, there is no conclusive proof that SARS-CoV-2 infects the myocardium resulting in myocarditis. Instead, the mechanism is probably one of immune-mediated damage and would justify steroids for treatment. However, many COVID-19 patients who were diagnosed with myocarditis do not meet the strict diagnostic criteria for the same, and giving steroids to such patients may be harmful[18-21].

Takotsubo cardiomyopathy: Takotsubo cardiomyopathy is an intriguing disorder, and its mechanism is yet to be elucidated fully. Takotsubo cardiomyopathy has been well documented in COVID-19 patients and can be due to the infection or the emotional stress associated with the pandemic[25]. Whether Takotsubo cardiomyopathy should be included as a cause of MINOCA is debatable. This is because the 'Fourth Universal Definition of Myocardial Infarction' does not consider Takotsubo cardiomyopathy a form of myocardial infarction[26]. On the other hand, the elevation of cardiac troponins is well documented in Takotsubo cardiomyopathy[27]. In our opinion, Takotsubo cardiomyopathy must be included in the diagnostic algorithm of MINOCA as there seems to be an increased incidence in COVID-19. Such a diagnosis carries certain therapeutic and prognostic implications as well.

Coronary vasculitis: Although coronary vasculitis is a rare cause of MINOCA, it has been reported in patients with COVID-19. Feuchtner *et al*[27] described an interesting case of a 48-year-old COVID-19 patient who was evaluated for chest pain and was found to have non-obstructive coronaries suggestive of MINOCA. However, further evaluation with CMR confirmed subendocardial inferior zonal late enhancement, and CTCA showed diffuse irregular vessel wall thickening and perivascular edema suggestive of vasculitis. The patient was managed with acetylsalicylic acid and clopidogrel and was discharged after cardiac enzyme levels declined. Postmortem studies showed COVID-19 viral inclusion bodies in endothelial cells, supporting the possibility of endothelial cell infection and endarteritis[28]. Hence, COVID-19 induced coronary vasculitis may be more common than currently reported. This case also underscores the importance of identifying patients with MINOCA and evaluating them further, rather than giving a presumptive diagnosis of myocarditis.

Spontaneous coronary artery dissection: Multiple case reports in COVID-19 patients have documented spontaneous coronary artery dissection[29-32]. The obstruction is caused by the separation of the medial and adventitial walls, with an intramural hematoma protruding into the lumen. It is hypothesized that there is an intrinsic underlying vasculopathy, and the dissection is precipitated by stress, catecholamine surge, physical activity, or sympathetic stimulation[33]. The underlying endothelial dysfunction and thrombo-inflammation may be the reason for coronary artery dissection occurring in COVID-19.

Coronary vasospasm: Diagnosis of coronary vasospasm in COVID-19 patients with MINOCA is challenging, but possible, if a systematic approach is followed. This was demonstrated by Rivero *et al* [34] in their case report of a 66-year-old man who presented with bilateral COVID-19 pneumonia and chest pain. After angiography, optical coherence tomography showed a stable, mainly fibrotic atheromatous plaque. The diagnosis of coronary vasospasm was clinched by administering intracoronary ergonovine at increasing doses which led to severe chest pain and universal ST-segment elevation. Coronary angiography done at this time revealed nearly occlusive coronary vasospasm involving both the left anterior descending coronary artery and left circumflex coronary artery. Given how challenging it is to diagnose coronary vasospasm, it may be another under-reported cause of MINOCA in COVID-19.

Miscellaneous causes: Type 2 myocardial infarction refers to events that occur due to a mismatch between myocardial oxygen supply and demand[26]. This is a heterogeneous class that can include various causes such as sepsis, anemia, arrhythmia, and pulmonary embolism-all of which can be seen in the setting of COVID-19 infection.

Evaluation of MINOCA

The differential diagnosis for MINOCA is broad, and therefore, a complete history and physical examination must remain at the core of its evaluation. It is also vital to re-take history and re-examine the patient multiple times at various stages of the evaluation process. This will ensure that investigations are directed appropriately and a 'fishing-expedition' approach is avoided. The initial set of investigations may give clues to the underlying diagnosis before more invasive tests are undertaken. In a prospective cohort of STEMI patients who underwent primary percutaneous coronary intervention

(PPCI) during the COVID-19 outbreak, patients with COVID-19 and MINOCA had elevated markers of inflammation and abnormal coagulation parameters[10]. Moreover, anti-phospholipid antibodies were observed in three of these patients.

Once obstructive coronary artery disease has been ruled out, the most important investigation for evaluating the cause of MINOCA is CMR[35]. A large prospective multicenter observational study conducted from 2007 to 2011 included 152 patients with MINOCA. In this study, CMR showed that 19% of the patients had signs of myocardial necrosis, 7% had signs of myocarditis, and 7% had unrecognized hypertrophic cardiomyopathy or could not be classified[36]. A meta-analysis of 34 studies with 199 COVID-19 patients for whom CMR was performed showed abnormal results in 79% and myocarditis in 40.2%[37]. A caveat is that the absence of myocardial necrosis on CMR does not exclude MINOCA as they may have other findings that support the diagnosis[38].

Prognosis

While the prognosis of MINOCA depends on the underlying disease, most studies to date indicate a better prognosis for MINOCA when compared to patients with AMI due to obstructive CAD[2]. A review of ST-elevation in COVID-19 patients observed an overall in-hospital mortality of 30%, with no significant difference between obstructive and non-obstructive CAD[17]. This is comparable with the mortality rate of 37.5% in our review. The effect of anti-viral therapy for MINOCA on COVID-19 is debatable. While none of the patients who died received anti-viral therapy, the small sample size and study designs preclude us from drawing definite conclusions[39,40]. As more cases of MINOCA are reported, it may be feasible to conduct well-designed prospective studies to explore these questions further.

LIMITATIONS

There are several limitations to this review. Many cases of MINOCA may have been treated along the lines of COVID-19 associated myocarditis. Therefore, it is likely that MINOCA is grossly under-reported in the literature. The small sample size of this review, due to the under-reporting of cases and the rarity of this condition, limits the generalizability of our findings. The publication of challenging cases with a positive outcome may have led to publication bias. There is also a lack of uniformity in the evaluation and diagnosis of MINOCA in COVID-19[41].

CONCLUSION

This review highlights that MINOCA in COVID-19 has a broad differential diagnosis that must be evaluated with a systematic diagnostic algorithm. COVID-19 patients with MINOCA had a mean age of 61.5 years, and 50% of them were men. The most common presenting symptom was chest pain (62.5%), and ST-elevation was present in most patients (87.5%). The overall mortality rate was 37.5%. More studies are required to arrive at a reliable estimate of the true prevalence and prognostic relevance of MINOCA.

FOOTNOTES

Author contributions: John K and Mishra AK contributed to the conceptual design of the study; John K and Mishra AK independently screened the articles and extracted the data; John K, Mishra AK, and Lal A contributed to the write-up and submission of the study; Mishra AK and Lal A reviewed the final manuscript; All authors reviewed and agreed with the final content of the article.

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Country/Territory of origin: United States

ORCID number: Kevin John 0000-0003-3382-0294; Amos Lal 0000-0002-0021-2033; Nitish Sharma 0000-0002-6221-3197; Amr ElMeligy 0000-0002-3053-0024; Ajay K Mishra 0000-0003-4862-5053.

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ORIGINAL ARTICLE

Case Control Study

Plasma D-dimer level in early and late-onset neonatal sepsis

Mohammed Al-Biltagi, Ehab M Hantash, Mohammed Ramadan El-Shanshory, Enayat Aly Badr, Mohamed Zahra, Manar Hany Anwar

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Mohammed Al-Biltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31511, Algharbia, Egypt

Mohammed Al-Biltagi, Department of Pediatrics, University Medical Center, Arabian Gulf University, Manama 26671, Manama, Bahrain

Mohammed Al-Biltagi, Department of Pediatrics, University Medical Center, Bahrain, Dr. Sulaiman Al Habib Medical Group, KSA, Manama 26671, Manama, Bahrain

Ehab M Hantash, Department of Anatomy, Faculty of Medicine, Tanta University, Tanta 31511, Alghrabia, Egypt

Ehab M Hantash, Neonatology Unit, Department of Pediatrics, Dr. Sulaiman Al Habib Medical Group, Riyadh 11636, Riyadh, Saudi Arabia

Mohammed Ramadan El-Shanshory, Department of Pediatrics, Hematol Unit, Tanta University, Faculty of Medicine, Tanta 31511, Algharbia, Egypt

Enayat Aly Badr, Mohamed Zahra, Department of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta 31511, Alghrabia, Egypt

Manar Hany Anwar, Department of Clinical Pathology, Ministry of Health, Egypt, Tanta 31511, Alghrabia, Egypt

Corresponding author: Mohammed Al-Biltagi, MBChB, MD, MSc, PhD, Chairman, Professor, Department of Pediatrics, Faculty of Medicine, Tanta University, Medical Complex, AlBahr Street, Tanta 31511, Algharbia, Egypt. mbelrem@hotmail.com

Abstract

BACKGROUND

Neonatal sepsis is a life-threatening disease. Early diagnosis is essential, but no single marker of infection has been identified. Sepsis activates a coagulation cascade with simultaneous production of the D-dimers due to lysis of fibrin. D-dimer test reflects the activation of the coagulation system.

AIM

To assess the D-dimer plasma level, elaborating its clinicopathological value in neonates with early-onset and late-onset neonatal sepsis.

METHODS

The study was a prospective cross-sectional study that included ninety neonates; divided into three groups: Group I: Early-onset sepsis (EOS); Group II: Late-onset sepsis (LOS); and Group III: Control group. We diagnosed neonatal sepsis according to our protocol. C-reactive protein (CRP) and D-dimer assays were compared between EOS and LOS and correlated to the causative microbiological agents.

RESULTS

D-dimer was significantly higher in septic groups with a considerably higher number of cases with positive D-dimer. Neonates with LOS had substantially higher levels of D-dimer than EOS, with no significant differences in CRP. Neonates with LOS had a significantly longer hospitalization duration and higher gram-negative bacteriemia and mortality rates than EOS ($P < 0.01$). Gram-negative bacteria have the highest D-dimer levels (Acinetobacter, Klebsiella, and Pseudomonas) and CRP (Serratia, Klebsiella, and Pseudomonas); while gram-positive sepsis was associated with relatively lower levels. D-dimer had a significant negative correlation with hemoglobin level and platelet count; and a significant positive correlation with CRP, hospitalization duration, and mortality rates. The best-suggested cut-off point for D-dimer in neonatal sepsis was 0.75 mg/L, giving a sensitivity of 72.7% and specificity of 86.7%. The D-dimer assay has specificity and sensitivity comparable to CRP in the current study.

CONCLUSION

The current study revealed a significant diagnostic value for D-dimer in neonatal sepsis. D-dimer can be used as an adjunct to other sepsis markers to increase the sensitivity and specificity of diagnosing neonatal sepsis.

Key Words: Early-onset neonatal sepsis; Late-onset neonatal sepsis; C-reactive protein; D-dimer

Core Tip: The study aimed to define the diagnostic and prognostic value of the D-dimer assay in early and late-onset sepsis. We prospectively studied C-reactive protein and D-dimer levels in 90 neonates divided into control, Early-onset sepsis, and late-onset sepsis. D-dimer was significantly higher in the septic groups, more in late-onset than early-onset sepsis, and with gram-negative sepsis than gram-positive sepsis. The best-suggested cut-off point for D-dimer in neonatal sepsis was 0.75 mg/L, giving a sensitivity of 72.7% and specificity of 86.7%.

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INTRODUCTION

Neonatal sepsis is a severe systemic inflammatory response to blood-stream infection with high morbidity and mortality during the neonatal period. Early and proper diagnosis of neonatal sepsis is critical for timely-administered antibiotics, decreases the length of the hospital stay, and improves the prognosis, especially the neurodevelopmental outcome[1]. To diagnose neonatal sepsis, the physicians usually depend on the blood culture, the gold standard, and some screening tools such as acute phase reactants and cytokines, for instance, the white blood cell count, C-reactive protein (CRP), procalcitonin, interleukin-6, interleukin-8, CD11b, and CD64. However, the blood culture yield is not always accurate, with the possibility of false-negative and positive results. Acute phase reactants and cytokines may have high sensitivity to diagnose bacterial sepsis, but they may lack high specificity and good predictive value[2,3].

As sepsis is a clinical condition resulting from the interaction between the microbial agent and the host immune, inflammatory, and coagulation responses, some studies showed changes in the circulating coagulation proteins coupled with impaired fibrinolytic activity in patients with confirmed sepsis[4]. Activation of the coagulation cascade resulting from the released sepsis-induced; inflammatory cytokines enhance the degradation of cross-linked fibrin polymers with increased production of D-dimer[5]. Consequently, D-dimer is considered a specific marker for increased procoagulatory activity and fibrinolysis. Elevation of D-dimer and fibrinogen degradation products rapidly occurs after dissem-

inated intravascular coagulation (DIC) initiation, which may arise as a complication of sepsis[6]. Activation of the coagulation reflected by the increase in D-dimer levels contributes significantly to the sepsis outcome. Different ways to assess D-dimer levels are available, including enzyme-linked immunofluorescence immunoassay, microplate enzyme-linked immunosorbent assay, latex quantitative, latex semiquantitative, latex qualitative, and whole-blood assays[7]. In this study, we aimed to assess the plasma level of D-dimer in infants with neonatal sepsis to throw more light on its clinicopathological value in patients having neonatal sepsis.

MATERIALS AND METHODS

The present research was a prospective cross-sectional study conducted on ninety-four full-term neonates recruited serially from the Neonatal Intensive Care Unit (NICU), Pediatric department; the tertiary care hospital of Tanta University between January 2019 to January 2021. The recruited neonates were divided into three comparable groups: Group I included neonates with early sepsis (who developed sepsis within the first week after childbirth), Group II included neonates with late neonatal sepsis (who developed sepsis within the first week after birth), and Group III included healthy neonates with no clinical manifestation of sepsis and negative CRP and Gerdes sepsis screen less than two, recruited from the postnatal ward of the Obstetric Department and the outpatient clinic. All parents, guardians, or next of kin signed informed consent for the minors to participate in this study. The Institutional Ethical and Research Review Board of the Faculty of Medicine, Tanta University, approved the study.

We diagnosed neonatal sepsis based on the presence of suspected clinical signs of sepsis, positive CRP (≥ 10 mg/L), positive Gerdes' sepsis screen (≥ 2), and positive blood culture. Sepsis was suspected in the presence of fever or temperature instability, irritability, lethargy, feeding difficulty, apnea or respiratory distress, hepatomegaly, abdominal distention, convulsion, hypotonia, hemodynamic instability, or bleeding diathesis. As the diagnosis of neonatal sepsis is hampered by the frequent presence of non-infectious conditions that may mimic sepsis, we only included those with proven sepsis and positive blood culture in the study. According to Neonatal Intensive Care Unit protocol, all children with suspected sepsis receive the appropriate management.

We excluded premature neonates and neonates with congenital heart diseases, hypoxic-ischemic encephalopathy, liver diseases, renal diseases, hereditary coagulopathy, or other non-sepsis-related systemic disorders that could affect the level of CRP or D-dimer levels. All included neonates had thorough prenatal, natal, and postnatal history, thorough clinical examination, complete blood cell count (CBC) with differential, CRP levels, urine analysis and culture, blood culture, cerebrospinal fluid (CSF) analysis, and culture, and other infection markers as indicated. Chest X-ray, echocardiography, or abdominal X-ray were tailored according to the clinical indications. The D-dimer assay was performed using the D-dimer test device (NycoCard D-dimer, Axis-Shield, Oslo, Norway) and the Nycocard READER II (NycoCard READER II, Axis-Shield, Oslo, Norway). It is a single rapid test for detection of D-dimer in plasma and is based upon an immunometric flow-through, sandwich-format, immunofiltration principle. CRP levels were measured using high-sensitive Tinaquant CRP (Latex) immunoturbidimetric assay using Roche Modular P analyzer (CRP latex HS, Roche kit; Roche Diagnostics, GmbH, D-68298 Mannheim, Germany), following the manufacturer's instructions.

Statistical analysis

We used the Power and Precision V3 program to estimate the power level of the primary endpoint (serum level of D-dimer with a mean level of 1.0 ± 0.3 mg/L) (http://www.Power-Analysis.com, Englewood, New Jersey). The power level was 90% when using 30 patients for each group. The collected data were organized, tabulated, and statistically analyzed using SPSS version 19 (Statistical Package for Social Studies, IBM, Chicago, IL, United States). For numerical values, the range means and standard deviations were calculated. The differences between the two mean values were used using the student's *t*-test. Differences in mean values between more than two groups were tested by analysis of variance (F). We used the Scheffe test to compare every two groups when we found significance. The number and percentage were calculated for categorical variables, and differences between subcategories were tested by chi-square. Fisher and Monte Carlo exact tests were used when chi-square was not appropriate. We used the receiver operating characteristic (ROC) test to evaluate the diagnostic power of the different diagnostic techniques. We used Pearson's correlation coefficient to test the relations between two variables. Sensitivity, specificity, and predictive values were calculated to differentiate the ability to diagnose sepsis by CRP, Gerdes, and I/T ratio. We adopted the level of significance at $P < 0.05$.

RESULTS

Figure 1 shows the flow chart of the study, which included three groups: the control group (30 healthy

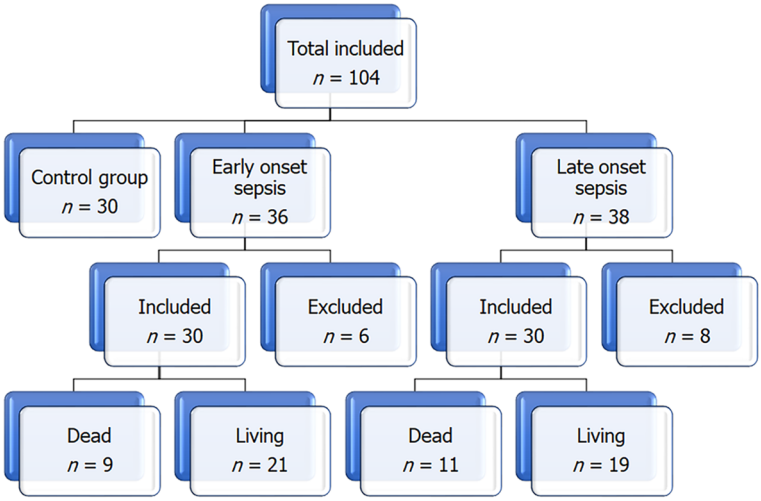

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Figure 1 The flow chart of the study.

neonates), Neonates with EOS (30 neonates after exclusion of 36 neonates), and neonates with LOS (30 neonates after exclusion of 8 neonates). The neonates were recruited sequentially. Table 1 and Figure 2 show the groups' demographics, clinical presentation, and laboratory testing. There were no significant differences between the groups in the male-to-female ratio, presentation weight, and cesarean section rate. However, LOS was more common in males than females. We found no significant differences in the clinical presentation between EOS and LOS, although respiratory distress was more common in the EOS while cyanosis was more common in LOS. However, the number of neonates with a positive Gerdes score (≥ 2) was significantly higher in the EOS than in LOS. Premature rupture of membranes was present in 20% of cases with EOS. While umbilical vein catheterization or endotracheal intubation was more common in EOS, combined umbilical vein catheterization and endotracheal intubation were significantly more common in LOS. Neonates with EOS had a substantially higher rate of thrombocytopenia than LOS. However, Neonates with LOS had considerably higher levels of D-dimer than EOS. Meanwhile, we found no significant differences in CRP levels in neonates with EOS or LOS. However, neonates with LOS had a significantly longer duration of hospitalization and higher mortality rates than neonates with EOS.

Table 2 shows the microbial profile of neonates with EOS and LOS. The gram-negative bacteremia rate was significantly higher in LOS than in EOS, while gram-positive bacteremia was markedly higher in EOS than in LOS ($P < 0.01$). *Klebsiella* was the most common isolated gram-negative organism, while *Group B Streptococcus* was the most common isolated gram-positive organism. Table 3 shows the blood levels of D-dimer and CRP according to the isolated organism, with gram-negative bacteria having the highest levels of D-dimer (*Acinetobacter, Klebsiella, and Pseudomonas*) and CRP (*Serratia, Klebsiella, and Pseudomonas*). On the other hand, gram-positive sepsis was associated with relatively lower levels of D-dimer and CRP. Table 4 showed that D-dimer had a significant negative correlation with hemoglobin level and platelet count while having a significant positive correlation with CRP, duration of the hospital stays, and mortality. The D-dimer levels were non-significantly higher in the neonates who died (1.91 ± 1.72) than those who survived (1.81 ± 1.68). We used the ROC curves to evaluate D-dimer's diagnostic power (discriminative ability) to diagnose neonatal sepsis. It revealed a significant diagnostic value for D-dimer for neonatal sepsis. The best-suggested cut-off point for D-dimer in neonatal sepsis is 0.75 mg/L, giving a sensitivity of 72.7% and specificity of 86.7% (Table 5).

DISCUSSION

The current study examined D-dimer yield in diagnosing neonatal sepsis in 90 neonates, divided into three groups, early-onset, last onset sepsis, and a control group. Despite there being no significant differences in gender among the studied group, we observed an increased rate of LOS in males than in females, which could be related to a diminished cell-mediated immune response in males as it is an X-chromosome-linked trait with the expression of some sex-specific pro-and anti-inflammatory cytokines [8].

D-dimers are the D fragments of fibrinogen resulting from fibrinolysis during the plasmin mediated lysis of fibrin and are more specific than fibrin/fibrinogen degradation products and can serve as an indicator of microcirculatory failure[9]. In the current study, we found a significant increase in serum level of D-dimer in both patient groups with sepsis compared to the control, being significantly higher

Table 1 The control and patients' demographic and clinical and laboratory data

		Control group (*n* = 30)	EOS group (*n* = 30)	LOS group (*n* = 30)	*t*/*Z*	*P* value
Age (mean ± SD, d)		2.10 ± 0.8	2.47 ± 0.57	12.47 ± 4.03	147.024	0.001
Weight (mean ± SD, g)		2.98 ± 0.4	2.85 ± 0.41	2.95 ± 0.3	0.895	NS
Male: Female		0.9:1	0.87: 1	1.5:1	0.356	NS
% of cesarean section		23 (76.7%)	22 (73.3%)	21 (70%)	0.381	NS
PROM		0	6 (20%)	0		
Risk factors (invasive procedure)	UVC	0	4 (13.3%)	0		0.001
	ETT	0	5 (16.7%)	4 (13.3%)		0.001
	UVC + ETT	0	7 (23.3%)	13 (43.3%)		0.001
	None	100%	14 (46.7%)	13 (43.3%)		0.001
Respiratory distress		0	27 (90%)	23 (77%)	1.920	NS
Apnea		0	3 (10%)	3 (10%)	FE	NS
Cyanosis		0	10 (33.3%)	14 (46.7%)	1.111	NS
Positive Gerdes score (≥ 2)		0	22 (73.3%)	19 (63.3 %)	38.258	0.001
Thrombocytopenia		2 (6.7%)	22 (73%)	12 (40%)	6.787	0.009
CRP (mg/dL)		4 ± 2	57.53 ± 38.82	65.47 ± 39.62	0.783	NS
D-dimer (mg/L)		0.60 ± 0.70	1.48 ± 1.44	2.27 ± 1.86	10.512	0.001
Hospital duration		0	21.6 ± 10	22 ± 9	0.051	NS
Mortality		0	9 (30%)	11 (36.7%)	0.300	NS

ETT: Endotracheal intubation; PROM: Premature rupture of membranes; UVC: Umbilical vein catheterization; NS: Not significant.

Table 2 Microbial profile in the patients' groups

		EOS group (*n* = 30)	LOS group (*n* = 30)	Total (*n* =60)	*t*	*P* value
Gram-negative bacteria	Total	21 (70.0%)	28 (93.3%)	49 (81.67%)	2.3	< 0.01
	Klebsiella	15 (50%)	20 (67%)	35 (58%)	1.3	NS
	E. coli	4 (13.30%)	1 (3.3%)	5 (8.33%)	-1.4	NS
	Acinetobacter	2 (6.66%)	4 (13.30%)	6 (10%)	0.85	NS
	Serratia	0%	1 (3.3%)	1 (1.66%)		
	Pseudomonas	0%	2 (6.66%)	2 (3.33%)		
Gram-positive bacteria	Total	8 (26.7%)	2 (6.7%)	10 (16.7%)	-2.07	< 0.01
	Group B Streptococcus	5 (16.60%)	0%	5 (8.33%)		
	CoNS	2 (6.66%)	1 (3.3%)	3 (5%)	-0.6	NS
	Enterococcus	1 (3.3%)	0%	1 (1.66%)		
	MRSA	0%	1 (3.3%)	1 (1.66%)		
Candida		1 (3.3%)	0%	1 (1.66%)		

EOS: Early-onset sepsis; LOS: Late-onset sepsis; *E. coli*: *Escherichia coli*; *CoNS*: *Coagulase-negative staphylococci*; *MRSA*: *Methicillin-resistant Staphylococcus aureus*; NS: Not significant.

in the LOS than the EOS. These findings agree with Peker *et al*[10] and Mautone *et al*[11], who found high D-dimer levels in neonates with sepsis. These results contrast with Brahmana *et al*[12], who found low D-dimer in neonates with sepsis. This difference could be related to the gestational age of the neonates recruited, as they included preterm babies in their study.

Table 3 Comparing D-dimer and C-reactive protein levels according to the isolated organisms

Organism		D-dimer (mean ± SD)	CRP (mean ± SD)
Gram-negative bacteria	*E. coli*	1.3 ± 0.81	44.2 ± 4.3
	Klebsiella	2.0971 ± 1.98916	71.1 ± 3.9
	Acinetobacter	2.1333 ± 1.63	37.7 ± 3.4
	Pseudomonas	1.95 ± 0.92	64.0 ± 5.65
	Serratia	1.8 ± 0.4	99.0 ± 0.79
Gram-positive bacteria	*Group B Streptococcus*	1.6 ± 10.6	39.7 ± 2.5
	CoNS	1.3 ± 0.51	53.7 ± 2.7
	MRSA	1.2 ± 0.60	58.0 ± 8.2

CRP: C-reactive protein; *E. coli*: *Escherichia coli*; *CoNS*: *Coagulase-negative staphylococci*; *MRSA*: *Methicillin-resistant Staphylococcus aureus*.

Table 4 Correlation between D-Dimer and other variables

Variables	D-dimer	
	R	*P* value
Hemoglobin	-0.246	0.020[1]
Platelets	-0.228	0.031[1]
CRP	0.249	0.018[1]
Duration of the hospital stays	0.4	0.001[1]
Mortality	0.43	0.001[1]

[1]Significant.
CRP: C-reactive protein.

Table 5 Recipient observer characteristics curve results for D-dimer to diagnose neonatal sepsis

ROC curve results	The area under the curve	*P* value	Cut off point	Sensitivity	Specificity
D-dimer (mg/L)	0.822	0.001	0.75	72.7%	86.7%

ROC: Receiver operating characteristic.

Our study found that D-dimer has a high sensitivity (72.7%) and specificity (86.7%) to diagnose neonatal sepsis with a cut-off point of 0.822 mg/L. This finding agrees with the work of Pancham *et al* [13], who found that D-dimer had a sensitivity (90.0%) and negative predictive value (84.4%) in predicting sepsis. Considering the relatively high sensitivity of D-dimer, it can be beneficial as an additional diagnostic tool for neonatal sepsis. However, we should consider the relatively low specificity of the D-dimer. The current study observed that D-dimer was higher in the LOS than in neonates with EOS. The increase of D-dimer in LOS than EOS may be related to increased frequency of gram-negative bacterial sepsis and rate of invasive procedures such as umbilical vein catheterization and endotracheal intubation compared to EOS, as we observed a significant increase of D-dimer plasma levels in gram-negative sepsis when compared to EOS. Previous studies showed that the inflammatory cytokines, reflecting the severity of infection, increased from 1.5-5 folds in gram-negative sepsis compared to gram-positive sepsis[14]. Unfortunately, we did not find previous studies comparing D-dimer levels between gram-negative and gram-positive sepsis. Meini *et al*[15] found that the D-dimer level can predict the severity and the course of severe invasive infections caused by the gram-negative bacteria *Neisseria meningitides* while failing to expect the course of the disease in invasive infections caused by *Streptococcus pneumoniae*. The increased rate of invasive procedures in LOS compared to EOS in our study could be an effect rather than a cause due to the increased rate of gram-negative sepsis with increasing severity. Meanwhile, there were higher rates of maternal risk factors such as premature rupture of membranes in the neonates with EOS than with LOS in our study. This finding could explain

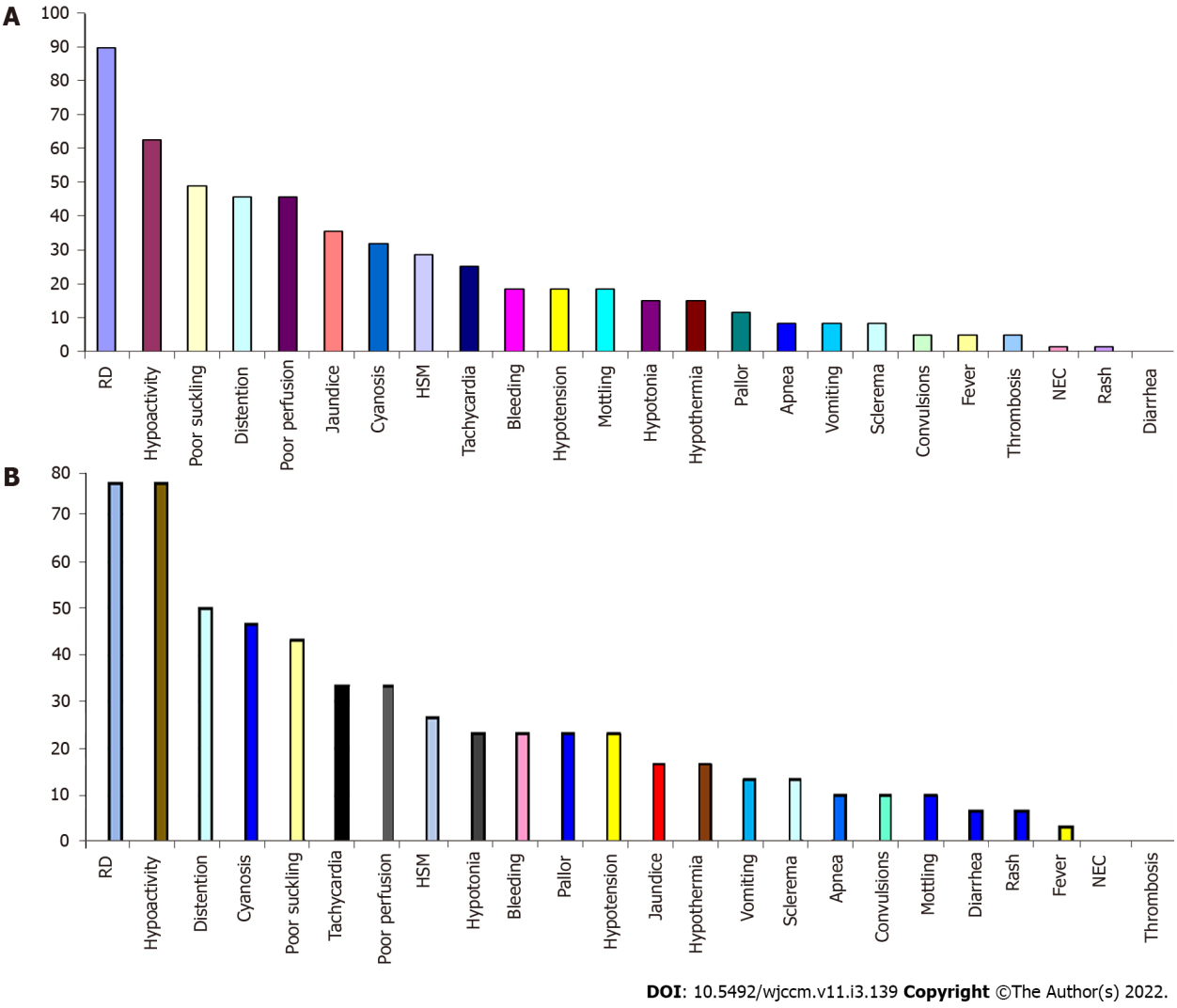

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Figure 2 The groups' demographics, clinical presentation, and laboratory testing. A: Frequency (%) of manifestations of sepsis in patients with early-onset sepsis; B: Frequency (%) of manifestations of sepsis in patients with late-onset sepsis.

why gram-positive sepsis was relatively more common in EOS than in LOS.

In the current study, we observed a significant positive correlation of D-dimer with CRP level, duration of hospitalization, and mortality rate. CRP is a marker of inflammation and plays a role in the inflammatory process itself, activating the complement pathway, phagocytosis, apoptosis, and the production and release of cytokines[16]. CRP evaluation has a role in neonatal sepsis diagnosis even though many studies showed low or at least variable validity in screening neonatal sepsis and being a non-specific test[17,18]. However, it is a good indicator of the success of the antibiotic treatment[19]. The addition of D-dimer to CRP can increase the sensitivity and specificity of both tests in the diagnosis of neonatal sepsis. We also observed a significant positive correlation of the level of D-dimer with the duration of hospitalization, which agrees with the results of previous studies[20,21]. The positive correlation of D-dimer level with the mortality rate observed in the current research is related to many factors, as high D-dimer is observed in gram-negative sepsis, which carries high mortality risk and is associated with elevated CRP, indicating the severity of inflammation.

The high mortality observed in the current study is related to the high percentage of gram-negative sepsis included in the study. Our NICU is the leading tertiary NICU in the region, receiving critically sick and septic neonates from peripheral units. Most of the isolated gram-negative organisms were Acinetobacter and Klebsiella; most were MDR. Meanwhile, many neonates had severe thrombocytopenia and markedly elevated CRP, which predict a worse prognosis. Our results agree with the meta-analysis done by Shah *et al*[22]. They found that patients with COVID-19 infection and elevated D-dimer levels had a higher risk of severe morbidity and mortality. Our results also agree with Ay *et al*[23], who found that a high D-dimer level was associated with a poor survival rate and high mortality rate in patients with cancer.

In the current study, we found a significant negative correlation of D-dimer with both hemoglobin (%) and the platelet count. Platelets have an active role in the host defense mechanisms as they can

perform phagocytosis. Their activation helps generate cytotoxic free radicals and oxidative molecules that destroy the invading organisms[24]. The current study found thrombocytopenia in 73% and 40% of EOS and LOS, respectively. Thrombocytopenia could be one of the presenting signs of neonatal sepsis but lack sensitivity and specificity and may appear late in the disease, which questions its usefulness as an initial marker of neonatal sepsis. However, we found a significant negative correlation between platelet count and plasma D-dimer levels. This correlation could reflect early or developing DIC, linked to increased fibrin degradation products (FDP) and D-dimer levels and increased platelet consumption [25]. Other possible causes of neonatal sepsis-associated thrombocytopenia could be increased platelet activation, diffuse endothelial cell injury, and bacterial/fungal toxins-associated platelet destruction [26]. Our results agree with Ree *et al*[27]. They reported that thrombocytopenia is independently associated with intravascular thrombosis and gram-negative sepsis, increasing the mortality risk nearly four to six-fold, especially in gram-negative sepsis.

Limitations

We have some limitations in the current study. We had a relatively small sample size. At the same time, the study was conducted in a single institution, so the results could not be generalized.

CONCLUSION

Neonatal sepsis is a life-threatening disease with high mortality and morbidity. The D-dimer is an exciting and promising biomarker for neonatal sepsis, able to predict morbidity and mortality. The current study revealed a significant diagnostic value for the D-dimer in neonatal sepsis. D-dimer can be used as an adjunct to other sepsis markers to increase the sensitivity and specificity of diagnosing neonatal sepsis.

ARTICLE HIGHLIGHTS

Research background

Neonatal sepsis is one of the critical conditions that put the life of neonates in danger. It is a severe systemic inflammatory response to blood-stream infections with significant neonatal morbidity and mortality. Early and proper diagnosis of neonatal sepsis is critical for timely-administered antibiotics, decreases the length of the hospital stay, and improves the prognosis, especially the neurodevelopmental outcome.

Research motivation

Early and proper diagnosis of neonatal sepsis is critical for appropriate and effective management with timely-administered antibiotics to decrease the hospitalization length and improve the prognosis, especially for the neurodevelopmental prospects.

Research objectives

We aimed to evaluate the significance of plasma D-dimer level in the early diagnosis of neonatal sepsis and elaborate on its clinicopathological value in neonates with early-onset and late-onset neonatal sepsis.

Research methods

The study was a prospective cross-sectional study that included ninety neonates; divided into early-onset sepsis (EOS) group (Group I), late-onset sepsis (LOS) group (Group II), and control group (Group III). We diagnosed neonatal sepsis according to our protocol. C-reactive protein (CRP) and D-dimer assay were compared and related to the causative microbiological agents.

Research results

D-dimer was significantly higher in septic groups. Septic groups showed a significantly higher number of cases with positive D-dimer. Neonates with LOS had considerably higher levels of D-dimer than EOS. At the same time, there were no significant differences in CRP levels in neonates with EOS or LOS. However, neonates with LOS had a significantly longer duration of hospitalization and higher mortality rates than neonates with EOS. The rate of gram-negative bacteremia was substantially higher in LOS than in EOS, while the rate of gram-positive bacteremia was significantly higher in EOS than in LOS ($P < 0.01$). Gram-negative bacteria have the highest D-dimer levels (Acinetobacter, Klebsiella, and Pseudomonas) and CRP (Serratia, Klebsiella, and Pseudomonas). On the other hand, gram-positive sepsis was associated with relatively lower levels of D-dimer and CRP. D-dimer had a significant negative correlation with hemoglobin level and platelet count while having a significant positive

correlation with CRP, duration of the hospital stays, and mortality. The best-suggested cut-off point for D-dimer in neonatal sepsis was 0.75 mg/L, giving a sensitivity of 72.7% and specificity of 86.7%. The D-dimer assay showed lower specificity and comparable sensitivity relative to CRP in the current study.

Research conclusions

The study revealed a significant diagnostic value for D-dimer in neonatal sepsis. D-dimer can be used as an adjunct to other sepsis markers to increase the sensitivity and specificity of diagnosing neonatal sepsis.

Research perspectives

To generalize our results, the authors need to include larger sample size and perform a multicenter study.

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FOOTNOTES

Author contributions: Anwar MH and El-Shanshory MR performed the clinical work and collected the data; Badr EA and Zahara MK performed the laboratory part; Hantash EM did the statistical analysis; Al-Biltagi M analyzed the data and wrote the manuscript; and All the authors revised and agreed to the final version of the manuscript.

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Informed consent statement: All parents, guardians, or next of kin signed informed consent for the minors to participate in this study.

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ORCID number: Mohammed Al-Biltagi 0000-0002-7761-9536; Ehab M Hantash 0000-0002-4164-6014; Mohammed Ramadan El-Shanshory 0000-0002-7995-8662; Enayat Aly Badr 0000-0002-9438-7255; Mohamed Zahra 0000-0002-1923-2659; Manar Hany Anwar 0000-0001-8927-2990.

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ORIGINAL ARTICLE

Retrospective Study

Stress cardiomyopathy in critical care: A case series of 109 patients

Parth Pancholi, Nader Emami, Melissa J Fazzari, Sumit Kapoor

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Parth Pancholi, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, United States

Nader Emami, Division of Critical Care Medicine, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, United States

Melissa J Fazzari, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, United States

Sumit Kapoor, Division of Critical Care Medicine, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, United States

Corresponding author: Sumit Kapoor, MD, Division of Critical Care Medicine, Department of Medicine, Montefiore Medical Center, Bronx, NY 10467, United States.
drkapoorsumit@gmail.com

Abstract

BACKGROUND

Critically ill patients are at risk of developing stress cardiomyopathy (SC) but can be under-recognized.

AIM

To describe a case series of patients with SC admitted to critical care units.

METHODS

We conducted a retrospective observational study at a tertiary care teaching hospital. All adult (≥ 18 years old) patients admitted to the critical care units with stress cardiomyopathy over 5 years were included.

RESULTS

Of 24279 admissions to the critical care units [19139 to medical-surgical intensive care units (MSICUs) and 5140 in coronary care units (CCUs)], 109 patients with SC were identified. Sixty (55%) were admitted to the coronary care units (CCUs) and forty-nine (45%) to the medical-surgical units (MSICUs). The overall incidence of SC was 0.44%, incidence in CCU and MSICU was 1.16% and 0.25% respectively. Sixty-two (57%) had confirmed SC and underwent cardiac catheterization whereas 47 (43%) had clinical SC, and did not undergo cardiac catheterization. Forty-three (72%) patients in the CCUs were diagnosed with primary SC, whereas all (100%) patients in MSICUs developed secondary SC. Acute respiratory failure that required invasive mechanical ventilation and shock developed in twenty-nine (59%) MSICU patients. There were no statistically significant differences in

intensive care unit (ICU) mortality, in-hospital mortality, use of inotropic or mechanical circulatory support based on type of unit or anatomical variant.

CONCLUSION

Stress cardiomyopathy can be under-recognized in the critical care setting. Intensivists should have a high index of suspicion for SC in patients who develop sudden or worsening unexplained hemodynamic instability, arrhythmias or respiratory failure in ICU.

Key Words: Stress cardiomyopathy; Critical care; Shock; Respiratory failure

Core Tip: In our retrospective study, we found that stress cardiomyopathy (SC) is often under-recognized in the critical care setting. Primary SC is commonly seen in the coronary care units and the secondary form predominates in the medical-surgical intensive care unit setting. Presentation of secondary SC is often atypical and the majority of patients have simultaneous acute respiratory failure and sepsis. High index of clinical suspicion for SC is needed in patients who develop sudden or worsening unexplained hemodynamic instability, arrhythmias or respiratory failure. Cardiac catheterization may not be always feasible to confirm the diagnosis. Routine utilization of point of care ultrasound on all intensive care unit patients will help identify more cases. The outcomes of these patients are excellent as majority of them show reversibility of cardiac function on follow up imaging.

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INTRODUCTION

Stress cardiomyopathy (SC) or Takotsubo cardiomyopathy or broken heart syndrome, was first described three decades ago in Japan[1]. It is characterized by acute and transient (< 21 d) left ventricular systolic and diastolic dysfunction, often precipitated by emotional or physical stress[1-6]. The diagnosis is usually made by modified Mayo Clinic criteria comprising of echocardiographic pattern of left ventricular apical hypokinesia, akinesia, or dyskinesia (apical ballooning) and basal hyperkinesis, electrocardiogram (EKG) changes (ST segment elevation and/or T wave inversion), troponin elevation and clean coronaries during cardiac catheterization[7].

Primary or classic SC has a reported incidence of around 1%-2% in patients with a suspicion of acute coronary syndrome (ACS) and is usually precipitated by physical or psychological stress[1]. Secondary SC, on the other hand, usually develops in hospitalized medical, surgical and neurological patients who may be under the major stress of critical illness in the medical-surgical intensive care unit (MSICU) setting[2,3,6,8-24].

The diagnosis of secondary stress cardiomyopathy in critically ill intensive care unit (ICU) patients can be challenging, requires a high degree of clinical suspicion, and is often under-recognized and under-reported for a myriad of reasons[8]. First, ICU patients do not always present with or report typical cardiac symptoms such as chest pain, shortness of breath, and syncope as patients presenting from the community do[8]. Second, there are no established diagnostic criteria for secondary stress cardiomyopathy in ICU patients and extrapolation of 2008 modified Mayo criteria may not be ideal[8]. Third, cardiac catheterization cannot be routinely performed in critically ill patients to confirm the diagnosis[8]. Fourth, patients can present with atypical morphologic variants of stress cardiomyopathy and there can be overlap with other diagnoses like sepsis induced cardiomyopathy[25]. Lastly, various multicenter international registries' data did not include critically ill patients, thereby limiting understanding of the clinical presentation and outcomes of this disease in the ICU population[8].

Very few studies have reported the incidence, clinical features and outcomes of stress cardiomyopathy in the intensive care setting[3,9,10,12-19,25-27]. None of them compared characteristics and outcomes based on critical care unit [MSICU *vs* coronary care unit (CCU)]. The reported incidence of secondary stress cardiomyopathy in the ICU varies from 0.37% to as high as 28%[3,13,14,16,18,19]. Jo *et al*[15] described underlying malignancy, male sex, old age and high APACHE2 score as the predictors of in-hospital mortality in patients with stress cardiomyopathy.

The aim of our research was to describe the case series of patients with stress cardiomyopathy admitted to the critical care units (CCUs and MSICUs) and study their clinical presentation, complications, and outcomes.

MATERIALS AND METHODS

Study design

We performed a retrospective case series study where all adult (≥ 18 years old) patients with the diagnosis of Stress cardiomyopathy or Takotsubo cardiomyopathy admitted to the critical care units of three hospitals in the Montefiore Healthcare System were included. Electronic health records for the 5-year period from January 1, 2015, to December 31, 2019, were retrospectively analyzed incorporating Looking Glass Clinical Analytics (Streamline Health, Atlanta, GA) to identify the target population. Critical care units included two coronary care units (CCUs) and five medical surgical units (medical, surgical or neurosurgical ICUs). The study was approved by the Institutional Review Board of the Albert Einstein College of Medicine (IRB# 2019-10754) and waiver of informed consent was granted due to minimal risk. Data about patient demographics, baseline characteristics, laboratory values, hospital course, complications and outcomes were collected for patients admitted to the critical care units.

Study definitions

The diagnosis of stress cardiomyopathy was made by the ICU teams collectively using a combination of 2-dimensional echocardiography, cardiac enzymes, EKG changes, and in some cases, coronary angiography.

Confirmed SC: Patients with SC who underwent cardiac catheterization to prove the absence of underlying coronary artery disease.

Clinical SC: Patients with SC who did not undergo cardiac catheterization and diagnosis was made clinically using 2D-echocardiography, cardiac enzymes and EKG changes only.

Primary SC: Patients with SC presenting from the community with cardiac symptoms like angina, dyspnea or palpitations. Clinical presentation mimics ACS, often precipitated by physical or mental stress.

Secondary SC: Patients developing SC during the course of hospitalization with critical medical, surgical or neurosurgical illness.

Typical variant of SC: Echocardiography regional wall motion abnormality pattern showing apical akinesis with basal hyperkinesis (apical ballooning).

Atypical variant of SC: Echocardiography regional wall motion abnormality pattern showing midventricular, basal, focal, or global hypokinesia.

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR), whereas categorical variables were reported as counts and percentages. Associations between categorical variables and unit were tested *via* chi-square or Fisher's exact test, as appropriate. Distributional differences between critical care units (CCU *vs* MS/ICU) with respect to continuous variables were assessed *via* Wilcoxon Mann-Whitney tests. Cumulative incidence functions for hospital discharge from the time of SC diagnosis stratified by critical care unit to allow for the competing risk of in-hospital death were estimated and differences tested using Grey's test[28]. Cumulative incidence functions for in-hospital death from the time of SC diagnosis with a competing risk of hospital discharge alive were computed similarly. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, United States) by the biomedical statistician. A two-sided P value of 0.05 or less was considered statistically significant.

RESULTS

Incidence and baseline characteristics

Of 24279 admissions to the critical care units (19139 MSICU and 5140 in CCU) over the five-year study period, 109 patients with SC were identified. Sixty (55%) of them were admitted to the coronary care units and forty-nine (45%) to the medical-surgical units. The overall incidence of SC was 0.44%, incidence in CCU and MSICU was 1.16% and 0.25% respectively. Sixty-two (57%) had confirmed SC and underwent cardiac catheterization whereas 47 (43.1%) had clinical SC and did not undergo cardiac

catheterization. Forty-three (72%) patients in the CCUs were diagnosed with primary SC, whereas all (100%) patients in MSICUs developed secondary SC.

Overall, the mean (SD) age was 67.2 (14.2) years and 72% were females. Hypertension and Diabetes Mellitus were the most common comorbidities seen in 65 (60%) and 40 (37%) patients respectively. Patients in the CCUs had more hypertension compared to those in MSICUs (70% *vs* 47%, $P = 0.01$). Table 1 lists the baseline characteristics of the study patients, both overall and stratified by critical care unit (CCU *vs* MSICU).

Unit course, complications and outcomes

Shortness of breath was the most common presenting symptom seen in 55 (50%) of the patients overall. Twenty-seven (45%) patients in the CCU complained of chest pain compared to only eight (16%) in MSICUs. Acute respiratory failure that required invasive mechanical ventilation was seen in twenty-nine (59%) MSICU patients, as opposed to only fifteen (25%) in CCU. Twenty-nine (59%) of patients in medical-surgical units also developed shock compared to twelve (20%) of the cardiac patients. Septic shock was the most common type of shock in MSICUs *vs* cardiogenic shock in CCUs (47% *vs* 8%, $P < 0.001$).

All SC patients had transthoracic echocardiography performed, with only 12 (24.5%) in MSICU getting cardiac catheterization, compared to 50 (83.3%) CCU patients. The majority ($n = 87$, 80%) of the cases were of typical anatomical type with apical akinesia/hypokinesia and basal hyperkinesia (apical ballooning). Inotropic support was required in ten patients and mechanical circulatory support in three patients. Follow up echocardiogram was performed in sixty-nine (63.3%) patients, all of them had complete reversibility of cardiac function. Of 47 patients with clinical SC, 27 had follow up echocardiography; all of them showed return to baseline cardiac function. Table 2 presents the complications and outcomes of SC by type of unit (MSICU *vs* CCU).

There was a statistically significant difference in the cumulative incidence function of hospital discharge stratified by critical care unit (0.56 *vs* 0.24 at 7 d, $P = 0.01$) but non-significant for in-hospital deaths stratified by critical care unit ($P = 0.33$) (Figure 1). Median length of stay from time of SC diagnosis to unit discharge was 1 d (range, 0-14) in CCU *vs* 5 d (range, 1-24) in MSICU.

A total of fifteen patients died out of which eight deaths were in the critical care units. There were no statistically significant differences in the peak laboratory values of creatine phosphokinase (CPK), troponin and pro-BNP (pro-B-type natriuretic peptide) or outcomes like ICU mortality, in-hospital mortality, use of inotropic or mechanical circulatory support based on type of unit (MSICU *vs* CCU) or anatomical variant (typical *vs* atypical) (Tables 3 and 4).

DISCUSSION

To our knowledge, this is the largest case series describing the clinical presentation, complications and outcomes of patients with stress cardiomyopathy admitted to the critical care units (MSICUs and CCUs). The overall incidence of SC in our patients was 0.44%, incidence in medical-surgical ICU was 0.25%, all of them having developed secondary SC. The incidence of SC in medical-surgical units varies per previous published reports. One of the earlier studies done by Park *et al*[13] in 2005 screened 92 consecutive critically ill patients admitted to medical ICU by serial echocardiography on day 1, 3, and 7. They observed a high incidence (28%) of left ventricular apical ballooning (LVAB) in medical ICU patients with no cardiac diseases. Patients with LVAB had higher prevalence of sepsis, hypotension upon ICU admission, use of inotropes, pulmonary edema, cardiomegaly and lower mean 2-month survival compared to patients without LVAB. The higher incidence of SC reported in the Park *et al*[13] study is likely because the diagnosis was solely made based on echocardiographic findings without integrating EKG, cardiac enzymes and coronary angiogram findings. An Australian study showed a much lower incidence of silent LVAB of around 3.5% in their medical ICU without any association of negative outcomes with silent LVAB[27]. Another prospective single center study by Doyen *et al*[14] in medical ICU patients found a high incidence of secondary SC of 4.6%. Our reported incidence of 0.25% in MSICUs is lower than the prior studies, because of the prospective nature of those studies, where all patients got echocardiographic screening for SC upon ICU admission. Muratsu *et al*[18] conducted a retrospective study on 5084 patients in Japan over a 5-year period and found a low incidence of clinical Takotsubo cardiomyopathy of 0.37%; a majority of their SC patients had the diagnosis of sepsis and subarachnoid hemorrhage. This demonstrates that there are likely many cases of SC which go under-recognized since formal echocardiography is not performed on every patient in the ICU. However, use of routine point of care ultrasound (POCUS) on critically ill ICU patients will likely identify many more cases of SC.

Sepsis and acute respiratory failure were the most common ICU diagnoses of patients developing secondary SC in these studies, which is similar to our patients in the MSICUs[13,14,18]. Kleber *et al*[29] reported a 15% prevalence of stress cardiomyopathy in the setting of acute respiratory failure requiring mechanical ventilation.

Table 1 Patient baseline characteristics and presentation by unit

	Overall, *n* = 109	MSICU, (*n* = 49)	CCU, (*n* = 60)	*P* value[1]
Age (yr), mean (SD)	67.2 (14.2)	64.9 (14.4)	69 (13.7)	0.13
Female gender – *n* (%)	78 (71.6)	30 (61.2)	48 (80.0)	**0.04**
Race/Ethnicity – *n* (%)				0.37
White	30 (27.5)	17 (34.7)	13 (21.7)	
Black	20 (18.4)	9 (18.4)	11 (18.3)	
Hispanic	42 (38.5)	15 (30.6)	27 (45.0)	
Other	17 (15.6)	8 (16.3)	9 (15.0)	
Comorbidities – *n* (%)				
Diabetes mellitus	40 (36.7)	19 (38.8)	21 (35)	0.68
Hypertension	65 (59.6)	23 (46.9)	42 (70)	**0.01**
Coronary disease	13 (11.9)	5 (10.2)	8 (13.3)	0.77
Heart failure	7 (6.4)	4 (8.2)	3 (5)	0.70
Arrhythmia	14 (12.8)	4 (8.2)	10 (16.7)	0.25
Asthma	16 (14.7)	6 (12.2)	10 (16.7)	0.52
COPD	13 (11.9)	6 (12.2)	7 (11.7)	0.93
Obesity	10 (9.2)	3 (6.1)	7 (11.7)	0.51
CKD	14 (12.8)	8 (16.3)	6 (10)	0.33
ESRD	3 (2.8)	1 (2)	2 (3.3)	1.00
Cancer	23 (21.1)	10 (20.4)	13 (21.7)	1.00
Cirrhosis	6 (5.5)	5 (10.2)	1 (1.7)	0.09
HIV	2 (1.8)	1 (2)	1 (1.7)	1.00
Social risk factors – *n* (%)				
Alcohol use	25 (22.9)	13 (26.5)	12 (20)	0.42
Current smoker	15 (13.8)	4 (8.2)	11 (18.3)	0.17
Former smoker	36 (33)	21 (42.9)	15 (25)	0.05
Presenting symptoms- *n* (%)				
Chest pain	35 (32.1)	8 (16.3)	27 (45)	**0.001**
SOB	55 (50.5)	23 (46.9)	32 (53.3)	0.51
Shock	41 (37.6)	29 (59.2)	12 (20)	**< 0.001**
Reason for unit admission- *n* (%)				
Cardiac	44 (40.3)	0 (0.0)	44 (73.3)	**< 0.001**
Respiratory	14 (12.8)	9 (18.4)	5 (8.3)	0.54
Sepsis	24 (22.0)	19 (38.8)	5 (8.3)	**< 0.001**
GI	11 (10.0)	9 (18.4)	2 (3.3)	0.14
Neurological	7 (6.4)	6 (12.2)	1 (1.7)	0.04
Metabolic	4 (3.7)	3 (6.1)	1 (1.7)	0.32
Other	5 (4.6)	3 (6.1)	2 (3.3)	0.66

[1]Corresponds to chi-square or Fisher's exact test for association for categorical variables, Wilcoxon Mann-Whitney test for continuous variables. Data are summarized as mean (SD) or *n* (%), where *n* = available sample size. MSICU: Medical surgical intensive care unit; CCU: Coronary care unit; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; ESRD: End stage renal disease; HIV: Human immunodeficiency virus; SOB: Shortness of breath; GI: Gastrointestinal.

Table 2 Stress cardiomyopathy diagnosis, complications and outcomes by unit

	Overall, *n* = 109	MSICU, (*n* = 49)	CCU, (*n* = 60)	*P* value[1]
Confirmed SC	62 (56.9)	12 (24.5)	50 (83.3)	**< 0.0001**
Clinical SC	47 (43.1)	37 (75.5)	10 (16.7)	
Hospital day of diagnosis1; median [IQR]	2 [1-3]	3 [2-4]	1 [1-2]	**0.0002**
Diagnostic Studies – *n* (%)				
Cardiac catherization	62 (56.9)	12 (24.5)	50 (83.3)	**< 0.001**
Transthoracic echo	109 (100)	49 (100)	60 (100)	
Lowest ejection fraction – (%); median [IQR]	35 [28-40]	30 [30-40]	35 [30-45]	0.38
TTE anatomical variant- *n* (%)				
Atypical	22 (20.2)	12 (24.5)	10 (16.7)	0.31
Typical	87 (79.8)	37 (75.5)	50 (83.3)	
Type of SC- *n* (%)				**< 0.001**
Primary	43 (39.4)	0 (0.0)	43 (71.6)	
Secondary	66 (60.5)	49 (100.0)	17 (28.3)	
EKG Findings- *n* (%)				
Normal EKG	21 (19.2)	14 (28.6)	7 (11.7)	**0.03**
ST-Segment elevation	54 (49.5)	15 (30.6)	39 (65.0)	**< 0.001**
ST-Segment depression	4 (3.7)	2 (4.08)	2 (3.3)	1.00
T-Wave inversion	23 (21.1)	13 (26.5)	10 (16.7)	0.24
Other	25 (22.9)	14 (28.6)	11 (18.3)	0.25
Complications – *n* (%)				
ECMO/IABP use	3 (2.8)	1 (2.0)	2 (3.3)	1.00
Inotrope use	10 (9.2)	7 (14.3)	3 (5)	0.11
New arrythmia	14 (12.8)	5 (10.2)	9 (15.0)	0.57
AKI	37 (33.9)	21 (42.9)	16 (26.7)	0.08
RRT	14 (12.8)	4 (8.2)	2 (3.3)	0.41
Acute respiratory failure – *n* (%)				
Mechanical ventilation	44 (40.4)	29 (59.2)	15 (25.0)	**< 0.001**
NIPPV only	15 (13.8)	8 (16.3)	7 (11.7)	0.48
Shock – *n* (%)	41 (37.6)	29 (59.2)	12 (20.0)	**< 0.001**
Cardiogenic shock	14 (12.8)	5 (10.2)	9 (15.0)	0.46
Septic shock	28 (25.7)	23 (46.9)	5 (8.3)	**< 0.001**
Other shock	2 (1.8)	2 (4.1)	0 (0.0)	0.11
Follow-up echocardiogram- *n* (%)				
Repeat echo (% Total)	69 (63.3)	30 (61.2)	39 (65.0)	0.69
Reversibility (% Echo)	69 (100.0)	30/30 (100.0)	39/39 (100.0)	1.00
Clinical SC patients				
Repeat Echo (% Total)	27/47 (57.4)	21/47 (44.7)	6/47 (12.8)	0.01
Reversibility (% Echo)	27/27 (100.0)	21/21 (100.0)	6/6 (100.0)	1.00
Hospital outcomes – *n* (%)				
In-hospital mortality	15 (13.8)	9 (18.4)	6 (10)	0.27

ICU mortality	8 (7.3)	3 (6.1)	5 (8.3)	0.73

[1]*n* = 3 patients diagnosed prior to intensive care unit admission, corresponds to chi-square or Fisher's exact test for association for categorical variables, Wilcoxon Mann-Whitney test for continuous variables.
27 patients with clinical SC got follow up echocardiogram, reversibility seen in all of them. Data are summarized as median (IQR) or *n* (%), where *n* = available sample size. SC: Stress cardiomyopathy; MSICU: Medical surgical intensive care unit; CCU: Coronary care unit; EKG: Electrocardiogram; ECMO: Extracorporeal membrane oxygenation; IABP: Intraaortic balloon pump; AKI: Acute kidney injury; RRT: Renal replacement therapy; NIPPV: Non invasive positive pressure ventilation.

Table 3 Peak laboratory values by unit

	MSICU (*n* = 49)	CCU (*n* = 60)	*P* value[1]
Troponin-T (ng/mL)	0.42 [0.23-1.2]	0.87 [0.29-1.54]	0.11
CPK (U/L)	427 [148.5-1348.5]	276.5 [161-695]	0.48
Pro-BNP (pg/mL)	5395 [1458-15000]	3363.5 [944.5-15369]	0.72

[1]Corresponds to a Wilcoxon Mann-Whitney test. Data are summarized as median (IQR).
MSICU: Medical surgical intensive care unit; CCU: Coronary care unit; CPK: Creatine phosphokinase; Pro-BNP: N-terminal pro- brain natriuretic peptide.

Table 4 Peak laboratory values and outcomes of stress cardiomyopathy by anatomical variant

	Typical (*n* = 87)	Atypical (*n* = 22)	*P* value[1]
Lab findings- median (IQR)			
Troponin-T (ng/mL)	0.65 [0.23–1.57]	0.58 [0.25-0.94]	0.61
CPK (U/L)	297.5 [151-919]	278 [168-631]	0.94
Pro-BNP (pg/mL)	3722 [874-11932]	5599 [1608.5-17373.0]	0.29
Hospital complications- *n* (%)			
Inotrope use	8 (9.2)	2 (9.1)	1
ECMO/IABP use	2 (2.3)	1 (4.5)	0.5
RRT	3 (3.4)	3 (13.6)	0.1
Hospital outcomes- *n* (%)			
In-hospital mortality	12 (13.8)	3 (13.6)	1
ICU mortality	7 (8)	1 (4.5)	1

[1]Corresponds to a Wilcoxon Mann-Whitney test.
Data are summarized as median (IQR) or *n* (%), where *n* = available sample size. CPK: Creatine phosphokinase, Pro-BNP: N-terminal pro- brain natriuretic peptide; ECMO: Extracorporeal membrane oxygenation; IABP: Intraaortic balloon pump; RRT: Renal replacement therapy; NIPPV: Non invasive positive pressure ventilation.

We found that CCU patients mostly presented with primary SC from the community, many of them developing typical chest pain, shortness of breath and classic ST segment elevation on electrocardiogram.

It is reported that patients with secondary SC usually have an atypical presentation in the ICU, with the majority of them developing sudden or worsening unexplained shock/hemodynamic instability and shortness of breath[9,13,14,18,19]. Fifty-nine (59%) percent of our MSICU patients developed shock compared to 20% of CCU patients. In the prospective study by Doyen *et al*[14], 53.8% medical ICU patients developed cardiogenic shock. This is different from our findings as the most common type of shock in our study was septic shock. The likely explanation for this discrepancy is that 47% of our population in medical surgical ICUs had the diagnosis of severe sepsis and septic shock compared to 38% in the Doyen study.

The 2008 modified Mayo Clinic criteria and European Society of Cardiology (ESC) Heart Failure Association diagnostic criteria for stress cardiomyopathy require that patients have the absence of obstructive culprit coronary artery disease[30,31].

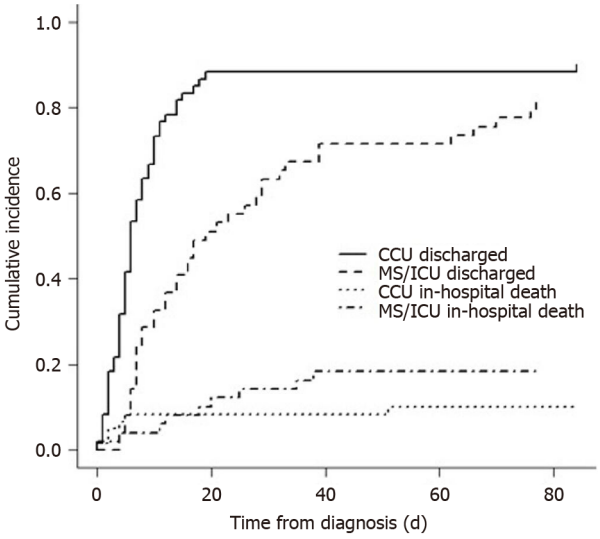

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Figure 1 Cumulative incidence function curve for hospital discharge *vs* death. *P* = 0.01 for hospital discharge stratified by type of unit, *P* = 0.33 for in hospital death stratified by type of unit.

However, there are many reasons for forgoing cardiac catheterization in the critically ill ICU patients, such as hemodynamic instability, multi-organ failure, risk of acute kidney injury (AKI) due to contrast induced nephropathy or established AKI amongst others.

Only 25% of our patients in medical-surgical units underwent cardiac catheterization, compared to 83% in the cardiac units. The mainstay of diagnosis of clinical SC in these critically ill patients was the combination of transthoracic echocardiography, cardiac enzymes and electrocardiogram findings.

Previous reports of SC in medical-surgical ICUs also relied mainly on transthoracic echocardiography along with cardiac enzymes and EKG changes for diagnostic purposes for similar reasons[13,14,18]. With the integration of POCUS as a routine diagnostic tool in the management of ICU patients, there will be an earlier recognition and an increase in the number of patients diagnosed with Stress cardiomyopathy at bedside by Intensivists, thereby improving care of these patients[32].

Patients with secondary SC in MSICUs also had longer ICU and hospital lengths of stay compared to CCU patients, primarily because MSICU patients were sicker with stressors such as acute respiratory failure, septic shock, neurologic disorders and multi system organ failure. Interestingly, we found that 11% (n = 12) of our cases developed SC in the perioperative setting. Agarwal *et al*[33] performed a systematic review of perioperative SC and found 102 cases in 93 articles. Management of our perioperative SC cases was similar to non-perioperative cases.

We report a low overall mortality for patients with SC. This is similar to prior studies that also report favorable outcomes of this patient population[3,9,10,13,14,18,19]. A relatively fast and complete recovery of cardiac function may explain this finding. Fifty-seven percent of our clinical SC patients had follow up echocardiogram, all showing reversibility of cardiac function, further supporting the diagnosis of SC. We also did not find any differences in mortality based on unit type (MSICU *vs* CCU) or anatomical type (typical *vs* atypical).

The major strength of our study is that we describe a large case series of patients with stress cardiomyopathy over the five-year period. We report and compare for the first time, characteristics, complications and outcomes of stress cardiomyopathy stratified by the type of unit and anatomical type. Our study has few limitations that need to be acknowledged. First, it is a single center study. Second, it is retrospective in nature and hence some data elements may not be captured accurately. Third, we believe that our incidence is likely underestimated, as many cases of SC may have gone unrecognized. Fourth, our definition of clinical SC could include cases of myocardial ischemia, showing improvement with development of collateral circulation. Fifth, follow up echocardiograms were only available in only 69 (63.3%) patients.

CONCLUSION

Stress cardiomyopathy can be under-recognized in the critical care setting. Primary stress cardiomyopathy is commonly seen in the CCUs and the secondary form predominates in the MSICU setting. Presentation of secondary SC is often atypical and the majority of patients have simultaneous acute respiratory failure and sepsis. Intensivists should have a high index of clinical suspicion for SC in patients who develop sudden or worsening unexplained hemodynamic instability, arrhythmias, or

respiratory failure. Many of the SC cases in MSICU may be diagnosed clinically as cardiac catheterization is not always feasible. Routine utilization of POCUS on all ICU patients will help identify more cases. The outcomes of these patients are excellent as majority of them show reversibility of cardiac function on follow up imaging.

ARTICLE HIGHLIGHTS

Research background

Critically ill patients are at risk of developing stress cardiomyopathy (SC) but can be under-recognized.

Research motivation

Our goal was to learn more about patients with SC in the intensive care unit (ICU) setting.

Research objectives

To study the patient characteristics, clinical course, and outcomes of critically ill patients with SC.

Research methods

We conducted a retrospective observational study at a tertiary care teaching hospital. All adult patients admitted to the critical care units with Stress cardiomyopathy over 5 years were included.

Research results

One hundred and nine patients were identified with SC, with 55% of them in the coronary care units (CCU) and 45% in the medical-surgical intensive care units (MSICUs). 57% of patients had SC confirmed by cardiac catherization while 43% were diagnosed clinically with echocardiography. 72% of CCU patients had primary SC whereas all MSICU patients had secondary SC. 59% of MSICU patients developed shock and acute respiratory failure that required mechanical ventilation. There were no statistically significant differences in ICU mortality, in-hospital mortality, use of inotropic or mechanical circulatory support based on type of unit or anatomical variant.

Research conclusions

Primary SC was commonly seen in the CCUs while secondary SC was seen more commonly in the MSICUs. Secondary SC often presents atypically and many patients have acute respiratory failure and sepsis. Many of the SC cases in the MSICU may be diagnosed clinically as cardiac catherization is not always feasible. Patients with SC in the ICUs have excellent outcomes with the majority of them showing reversibility of cardiac function.

Research perspectives

Stress Cardiomyopathy is often under-recognized in the critical care setting. In the MSICUs, secondary SC is the main form of SC encountered, where is it is often diagnosed clinically. Routine use of Point-of-care ultrasound may help with early identification of these cases.

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FOOTNOTES

Author contributions: Pancholi P contributed with data acquisition, data analysis, and manuscript writing; Emami N contributed with data acquisition, analysis and manuscript editing; Fazzari MJ performed the data analysis; Kapoor S designed the study, contributed to manuscript writing, and provided overall supervision; all authors have read and approve the final manuscript.

Institutional review board statement: The study was approved by the Institutional Review Board of the Albert Einstein College of Medicine (IRB# 2019-10754) and waiver of informed consent was granted due to minimal risk.

Conflict-of-interest statement: The authors report no conflicts of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author. Participant consent was not obtained but the presented data are anonymized and risk of identification is low.

Country/Territory of origin: United States

ORCID number: Parth Pancholi 0000-0002-1319-4882; Nader Emami 0000-0002-9001-9287; Melissa J Fazzari 0000-0002-5674-3589; Sumit Kapoor 0000-0002-5683-3445.

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Observational Study

Need for oxygen therapy and ventilatory support in premature infants in a hospital in Southern Brazil

Amanda Meier, Kelser de Souza Kock

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Amanda Meier, Kelser de Souza Kock, Department of Physiotherapy, University of South of Santa Catarina, Tubarão 88704-001, SC, Brazil

Corresponding author: Kelser de Souza Kock, PhD, Physiotherapist, Professor, Department of Physiotherapy, University of South of Santa Catarina, José Acácio Moreira Street-787, Tubarão 88704-001, SC, Brazil. kelserkock@yahoo.com.br

Abstract

BACKGROUND

Prematurity in newborns is a condition that is associated with worse hospital outcomes when compared to birth to term. A preterm infant (PI) is classified when gestational age (GA) < 37 wk.

AIM

To analyze prognostic indicators related to the use of oxygen therapy, non-invasive ventilation (continuous positive airway pressure) and mechanical ventilation (MV) in PI.

METHODS

This is a retrospective cohort. The sample was composed of PIs from a private hospital in southern Brazil. We included neonates with GA < 37 wk of gestation in the period of January 1, 2018 to December 31, 2018. For data collection, electronic records were used in the Tasy Philips™ system, identifying the variables: maternal age, type of birth, prenatal information, GA, Apgar score, birth weight, neonatal morbidities, vital signs in the 1st hour at birth, need for oxygen therapy, continuous positive airway pressure and MV, hospitalization in the neonatal intensive care unit, length of stay and discharge or death.

RESULTS

In total, 90 PI records were analyzed. The median (p25-p75) of GA was 34.0 (31.9-35.4) wk, and there were 45 (50%) males. The most common morbidity among PIs was the acute respiratory discomfort syndrome, requiring hospitalization in the neonatal intensive care unit in 76 (84.4%) cases. The utilization rate of oxygen therapy, continuous positive airway pressure and MV was 12 (13.3%), 37 (41.1%) and 13 (14.4%), respectively. The median (p25-p75) length of stay was 12.0 (5.0-22.2) d, with 10 (11.1%) deaths. A statistical association was observed with the use of MV and GA < 28 wk, lower maternal age, low birth weight, Apgar < 8 and neonatal deaths.

CONCLUSION
The identification of factors related to the need for MV in prematurity may help in the indication of a qualified team and technologies to promptly meet the unforeseen events that may occur after birth.

Key Words: Premature; Continuous positive airway pressure; Artificial respiration; Non-invasive ventilation

Core Tip: This is an observational study evaluating the need for oxygen therapy and ventilatory support in preterm infants. In our analysis, we present the odds ratio of the use of mechanical ventilation when compared to maternal and preterm epidemiological parameters.

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INTRODUCTION

Prematurity in newborns is a condition that is associated with worse hospital outcomes when compared to birth to term. However, in recent years there has been an increase in survival rates due to the improvement in neonatal intensive care, supported by technological evolution and the qualification of professionals in the field[1]. Even with all these progressions, prematurity rates at the present time remain high, reaching 10.94% of live births in 2018 in Brazil[2].

The determining gestational age of a preterm birth (PTB) is less than 37 wk, related to some resultants that generate the anticipation of childbirth[3]. Obstetric complications can interfere with the natural process of pregnancy, causing premature delivery, some of which are infections, hypertensive diseases, diabetes and hemorrhages that are more common[4]. According to DATASUS in Brazil in 2018 (its last census), the duration of pregnancy between 22 wk and 36 wk was 322234 live births, among them single, double, and triple births; in the South region there were 43313 live births[2].

Among the factors related to the clinical evolution of the PTB are gestational age (GA), Apgar score, weight at birth, congenital malformations/morbidities and vital signs. The Apgar scale is a tool for systematic assessment of the newborn, created by Virginia Apgar in 1953, for this reason the name Apgar. It uses a numerical score from 0 to 10, which has five variables, heart rate, respiratory effort, color, muscle tone and reflex irritability. It is used as an indicator of fetal distress if less than 5 on the scale is determined. Oxygen therapy (O2) is offered to reduce respiratory difficulty and collaborate in hemodynamic stabilization[5]. Newborns under 2500 kg have an increased risk of death in the 1st year of life and of developing infectious diseases, respiratory diseases, growth retardation and development[6]. Constant monitoring and early initiation of appropriate therapy prevent possible complications of disease and prematurity[7].

In Brazil, 24061 live births and 268 neonatal deaths were named, with a neonatal mortality rate of 11.1 deaths per thousand live births. Causes of neonatal death prevailed in the prematurity group, accounting for about one-third of the cases, followed by congenital malformation (22.8%), infections (18.5%), maternal factors (10.4%) and asphyxia/hypoxia (7%)[8].

At-risk birth, as in PTB, a physiological and/or hemodynamic imbalance occurs, where the extrauterine environment generates numerous adaptations involving morphophysiological and biochemical maturation of the lung parenchyma[9]. The inability to achieve effective breathing, lack of a powerful respiratory drive, reduced muscle strength, lack of surfactant and high compliance of the chest wall are contributing factors to respiratory failure[10]. As a result of these factors, premature babies need respiratory assistance to perform and/or adapt gas exchange and establish consistent functional residual capacity[10].

Several methods are used to provide respiratory support to premature infants, including intubation, prophylactic surfactant, oxygen therapy and non-invasive ventilation. Intubation requires all airway control, reducing support according to tolerance, with as little intubation time as possible, avoiding related morbidities. Surfactant administration is prophylactic, preventing lung damage and respiratory implications[11].

Due to the importance in early recognition of PTBs that will need ventilatory support, this work sought to analyze prognostic indicators related to the need for invasive mechanical ventilation in PTB[8, 12]. The use of maternal and newborn epidemiological parameters as well as physiological signs of the

premature infant in the first 24 h can be used as indicators for respiratory failure. In this sense, the general objective of this study was to analyze factors related to the need for ventilatory support in PTB in 2018 in a hospital in southern Brazil.

MATERIALS AND METHODS

This is a retrospective cohort type study. The sample was composed of premature infants in a private hospital in the city of Tubarão, Santa Catarina, Brazil. It has 8 beds in the neonatal intensive care unit, 10 adult beds in the intensive care unit, 50 adult inpatient beds and 21 adult and pediatric beds as required.

The following criteria were adopted for inclusion: newborns of both sexes and preterm born with less than 37 wk of gestation in the period from January 1, 2018 to December 31, 2018. The exclusion criteria were incomplete medical records and newborns transferred to another hospital. Electronic records were used in the Tasy Philips™ system for data collection.

This research project was approved by the Ethics Committee in Human Beings of UNISUL under the number of the opinion 3.529.438, CAAE: 17573519.2.0000.5369.

The following variables were extracted from the electronic records: gestational age, Apgar score, birth weight, congenital malformations/morbidities, vital signs at the first hour of birth, maternal age, type of delivery, previous adequate prenatal, mother's morbidity, number of gestations, use of O2, non-invasive ventilation [continuous positive airway pressure (CPAP)] and mechanical ventilation (MV), need for admission to the neonatal intensive care unit, length of stay and discharge or death.

The data were stored in a database created with the Excel® software and later exported to the SPSS 20.0® software. They were presented through absolute numbers and percentages, measures of central tendency and dispersion. A logistic regression analysis was performed to obtain the odds ratio in comparison to the use of mechanical ventilation. Considering the 95% confidence interval, a 5% statistical significance level was used.

RESULTS

We analyzed 90 PTB records and their maternal antecedents. Of these, 81 were cesarean deliveries and 45 (50%) were boys. The median (p25-p75) age of the mother was 31.0 (28.0-35.0) years, the most common comorbidity was premature rupture of membranes, and other comorbidities included fetal malformations and inadequate fluid in the amniotic sac. The highest frequency of prenatal visits was 4 to 7, which 64 women performed.

The median gestational age was 34.0 (31.9-35.4) wk, where the most common morbidity among the PTB was respiratory distress syndrome. The Apgar in the first and fifth minute were higher than 8 in the majority, where 37 needed CPAP and 13 needed orotracheal intubation. The need of admission to the neonatal intensive care unit occurred for 76 patients, where the median length of hospital stay was 12.0 (5.0-22.2) d, of which 10 deaths occurred, totaling 11.1% of the PTB. Tables 1 and 2 summarize the information from maternal data and PTB.

In the present study, lower maternal age, lower gestational age, lower birth weight, Apgar < 8 and death were statistically significant and were associated with patients who required MV compared to those who did not require oxygen support (Table 3).

DISCUSSION

Prematurity all over the world is an evident problem in perinatal health, and in Brazil it is one of the major causes of infant mortality. Preterm infants (PIs) are at an increased risk of adapting to life in the extrauterine environment, mainly due to the immaturity of the physiological and anatomical system[9, 13].

The main findings of the study showed that the need for MV is associated with extreme prematurity with gestational age < 32 wk, a lower maternal age, low birth weight, Apgar < 8 in the first and fifth minutes of life and neonatal deaths compared to PIs who did not use oxygen therapy. More than half of the studied PIs required some form of oxygen support, whether helmet or incubator O2, CPAP or MV.

Premature rupture of membranes is determined by the loss of amniotic fluid before birth. According to the Hackenhaar *et al*[14] study, that rupture may be associated with a pregnant woman's age above 29 years. The study explained that it may be related to endogenous changes in the fetus and its annexes. In the present study we noticed that one-third of the pregnant women had premature rupture of membranes as a comorbidity and that a little more than half of the women were older than 30 years.

Prenatal care should be initiated in the first trimester of pregnancy; a total of at least six consultations should be performed. During the consultations, physical examinations should be performed, and if necessary, specific tests should be performed. The early initiation of prenatal care provides access to

Table 1 Maternal data

	n (%)
Mother's age	
≤ 25 yr	9 (10.0)
> 25 and ≤ 30 yr	27 (30.0)
> 35 and ≤ 40 yr	20 (22.2)
> 40 yr	1 (1.1)
Maternal/gestational comorbidities	
PROM	30 (32)
Preeclampsia	11 (12.1)
UTI	8 (8.8)
HDP	6 (6.6)
HELLP Syndrome	2 (2.2)
DM	1 (1.1)
Others	32 (32.8)
Number of pregnancies	
1	50 (55.6)
2	31 (34.4)
3	6 (6.7)
4	3 (3.3)
Prenatal consultations	
< 4	2 (2.2)
4-7	64 (71)
≥ 8	24 (26.7)

PROM: Premature rupture of membranes; UTI: Urinary tract infection; HDP: Hypertensive disease of pregnancy DM: Diabetes mellitus; HELLP Syndrome: Hemolysis, elevated liver enzymes, low platelet count.

diagnostic and therapeutic methods to prevent possible pregnancy complications[14]. More than half of the pregnant women had 4 to 7 consultations, showing that consultations do not prevent prematurity but that a more thorough follow-up can prevent maternal and child complications.

Cesarean delivery was predominant in more than 85% of PIs, and most pregnancies were uniparous, according to the Miranda-Flores study[15]. Cesarean section is indicated in pregnancies from 26 wk to 31 wk + 6 d, and vaginal delivery in pregnancies under 26 and over 31, depending on maternal and fetal conditions, in which the cesarean section represents a higher percentage[15].

The median gestational age found was similar to the study by Galleta *et al*[16]. It is during this period that the formation of surfactant takes place by the type II pneumocytes, which are responsible for preventing the alveoli from collapsing when in contact with air. Newborn respiratory distress syndrome (NRDS) remains one of the most frequent complications in infants weighing 1500g or less.

The data in relation to neonatal death in this study are similar to the works of Lansky *et al*[8] and Andegiorgish *et al*[17]. In the study by Myrhaug *et al*[18], in infants born alive, the survival rate increased from 74.0% for infants born at 25 wk GA to 90.1% for those born at 27 wk GA. The study by Glass *et al*[19] reported the morbidity and mortality of 1765 PIs (birth weight 500-1500 g) in the period after implementation of neonatal intensive care units and mechanical respiratory support. In a meta-analysis evaluating the outcome in PIs, survival improved significantly with each week of GA and for each 100-g increase in birth weight. Specifically, survival in the 500-600 g group was only 20% compared to 56% in the 700-800 g birth weight group. It can be observed that in the studies there was a higher survival rate in infants with lower GA who had support in the neonatal intensive care unit where more and more medical and technological advances are showing a better prognosis regarding the prediction of ventilatory support[18]. In this study, it was observed that lower GA and low birth weight were associated with the use of MV, and this in turn was related to death.

Table 2 Preterm infant data

	Median (p25-p75)
Gestational Age (wk)	34 (31.9-35.4)
< 28, *n* (%)	7 (7.8)
≥ 28 and < 30, *n* (%)	5 (5.6)
≥ 30 and < 34, *n* (%)	27 (30.0)
≥ 34 and < 37, *n* (%)	51 (56.7)
Birth weight (grams)	2240.0 (1588.7-2520.0)
PI Morbidities, *n* (%)	
NRDS	55 (60.9%)
Low birth weight	5 (5.5%)
Tachypnea	4 (4.4%)
Apnea	1 (1.1%)
Others	25 (28.1%)
HR (bpm), 1st h after birth	145.0 (134.7-153.2)
RR (cpm), 1st h after birth	52.0 (41.7-64.0)
SpO2 (%)-1st h after birth	96.0 (93.0- 97.0)
Apgar (1st min)	8.0 (6.0-8.0)
< 8, *n* (%)	39 (43.2%)
≥ 8, *n* (%)	51 (56.7%)
Apgar (5th min)	9.0 (8.0-9.0)
< 8, *n* (%)	6 (6.6)
≥ 8, *n* (%)	84 (93.3%)
Need for oxygen therapy or ventilatory support	
Oxygen therapy	12 (13.3%)
CPAP	37 (41.1%)
MV	13 (14.4%)
ICU admission	76 (84.4%)
Length of stay (d)	12.0 (5.0-22.2)
Death	10 (11.1%)
Death by gestational age	
< 28 wk, *n* (%)	6 (6.7)
≥ 28 and < 30 wk, *n* (%)	0 (0.0)
≥ 30 and < 34 wk, *n* (%)	2 (2.2)
≥ 34 and < 37 wk, *n* (%)	2 (2.2)

PI: Preterm infant; ICU: Intensive care unit; NRDS: Newborn respiratory distress syndrome; HR: Heart rate; RR: Respiratory rate; SpO2: Peripheral oxygen saturation; CPAP: Constant positive airway pressure; MV: Mechanical ventilation.

The main morbidity found in PIs was NRDS. According to Sweet *et al*[20], NRDS is a significant problem for premature infants, and they sought to maximize survival with the creation of guidelines for better management of these patients. CPAP should be initiated from birth in all infants at risk of respiratory distress, such as those at < 30 wk GA who do not require intubation for stabilization. After stabilization, MV should be used in infants with respiratory distress when other methods of respiratory support fail. The duration of MV should be minimized whenever possible. To achieve the best outcomes for PIs with respiratory distress, optimal supportive care with monitoring of physiological variables is important. In the neonatal intensive care unit, there should be access to continuous pulse oximetry,

Table 3 Comparison of data according to the need for mechanical ventilation

	Ambient air-O2-CPAP Median (p25-p75) *n* (%) = 77 (85.6)	MV Median (p25-p75) *n* (%) = 13 (14.4)	OR (95%CI)	*P* value
Maternal age	32.0 (28.5 - 36.0)	28.0 (25.0 - 31.5)	0.823 (0.710-0.954)	0.010[a]
GA in wk	34.1 (33.1-35.4)	29.4 (25.4-32.0)	0.632 (0.504-0.790)	< 0.001[b]
< 28[1]	1 (14.3)	6 (85.7)	147.000 (11.527-1874.655)	< 0.001[b]
≥ 28 and < 30[1]	4 (80.0)	1 (20.0)	6.125 (0.451-83.116)	0.173
≥ 30 and < 34[1]	23 (85.2)	4 (14.8)	4.261 (0.727-24.970)	0.108
≥ 34 and < 37[1]	49 (96.1)	2 (3.9)	1.000	
Birth weight (g)	2260.0 (1707.5-2621.5)	1035.0 (605.0-1819.0)	0.997 (0.996-0.999)	< 0.001[b]
HR (bpm)	145.0 (135.0-153.5)	139.0 (129.5-155.0)	1.001 (0.970-1.032)	0.969
RR (com)	52.0 (41.0-64.0)	53.0 (46.5-64.5)	1.014 (0.971-1.059)	0.525
SpO2 (%)	93.0 (93.0-97.0)	96.0 (84.0-97.5)	0.975 (0.939-1.012)	0.178
Length of stay (d)	12.0 (5.0-21.0)	15.0 (1.5-39.0)	1.028 (0.990-1.067)	0.154
Apgar 1 min[1]				
< 8	28 (71.81)	11 (28.2)	9.625 (1.989-46.569)	0.003[a]
≥ 8	49 (96.1)	2 (3.9)	1.000	
Apgar 5 min[1]				
< 8	2 (33.3)	4 (66.7)	16.667 (2.666-104.189)	0.003[a]
≥ 8	75 (89.3)	9 (10.7)	1.000	
Outcome[1]				
Discharge	76 (95.0)	4 (5.0)	1.000	< 0.001[b]
Death	1 (10.0)	9 (90.0)	171.000 (17.185-1701.583)	

[1]*n* (%).

[a]*P* < 0.05.

[b]*P* < 0.001. GA: Gestational age; HR: Heart rate; RR: Respiratory rate; SpO2: Peripheral oxygen saturation; O2: Oxygen therapy; CPAP: Constant positive airway pressure; MV: Mechanical ventilation; OR: Odds ratio; CI: Confidence interval.

electrocardiogram monitoring and monitoring of PaCO2 levels.

Regarding vital signs in the first hour, no association was observed with the need for ventilatory support. According to the study by Kumar *et al*[21], where clinical assessment and nursing observation are very important, some vital sign data are not used and the update in the medical records can still be improved. Vital sign monitoring is constantly monitored on monitors at the incubator bedside. Short and long-term monitoring can predict sepsis risks and neurological and respiratory problems, as slowing heart rate may be indicative of some pathologies. Lower peripheral oxygen saturation (85%-89%) has a higher incidence of intermittent hypoxemia compared to higher peripheral oxygen saturation (91%-95%) during the first 3 d of life. Respiratory rate monitoring is important for detection of apnea associated with decreased heart rate and peripheral oxygen saturation. Perhaps, dynamic monitoring of vital signs could provide more prognostic information than those assessed only at the first hour.

The comparison of data from PIs with low Apgar scores at the fifth minute and birth weight less than 1500g are closely linked to the need for MV and neonatal mortality, corroborating the study by Dalili *et al*[22]. The study by Oliveira *et al*[23] states that mortality increased for those with Apgar scores 4-7 in relation to PIs weighing between 1500 g and 2999 g, which shows that the lower the birth weight, the higher the mortality. The Apgar score was the best known and oldest form of measurement of neonatal asphyxia. New knowledge, such as the determination of fetal blood pH, among others, has changed this concept, and the score of 6 or less at the fifth minute has become the most important reference in the diagnosis and prognosis of asphyxia, along with the proposal not to wait for the first minute score to start resuscitation maneuvers. Despite this, the first minute score still seems to have importance in the

prognosis of mortality[21,22].

Limitations found in this study were the small sample size, research conducted in a hospital that provides health care only to health insurance companies/private entities, and not being able to generalize the findings to other hospitals.

CONCLUSION

We conclude that the need for mechanical ventilation is associated with extreme prematurity with GA < 28 wk, lower maternal age, low birth weight, Apgar < 8 at the first and fifth minutes of life and neonatal deaths. NRDS is the most frequent morbidity in premature infants, where more than half of those studied required some form of oxygen support, whether O2, CPAP or MV. The identification of factors related to the need for MV in prematurity may help in the indication of a qualified team and technologies to promptly meet the unforeseen events that may occur after birth.

ARTICLE HIGHLIGHTS

Research background

Prematurity may be associated with some degree of respiratory failure.

Research motivation

Clinical recognition of premature infants at risk is important for appropriate management of ventilatory support.

Research objectives

To assess maternal and newborn factors related to the need for ventilatory support.

Research methods

A retrospective cohort conducted in a private hospital in southern Brazil consisted of preterm infants with gestational age < 37 wk.

Research results

We evaluated 90 premature infants with median (p25-p75) gestational age of 34.0 (31.9-35.4) wk. The utilization rate of oxygen therapy, continuous positive airway pressure and mechanical ventilation was 12 (13.3%), 37 (41.1%) and 13 (14.4%), respectively. The median (p25-p75) length of stay was 12.0 (5.0-22.2) d, with 10 (11.1%) deaths. A statistical association was observed with the use of mechanical ventilation and gestational age < 28 wk, lower maternal age, low birth weight, Apgar < 8 and neonatal deaths.

Research conclusions

The need for mechanical ventilation in premature infants was related to low birth weight, extreme prematurity and low Apgar.

Research perspectives

Other clinical indicators for predicting ventilatory support in premature infants can be used, such as monitoring vital signs and their variability measures.

FOOTNOTES

Author contributions: Meier A performed the data collection and wrote the manuscript; Kock KS performed the statistical analysis and revision and editing of the manuscript.

Institutional review board statement: This research project was approved by the Ethics Committee in Human Beings of (University of Southern Santa Catarina, Brazil) UNISUL under the number of the opinion 3.529.438, CAAE: 17573519.2.0000.5369.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Country/Territory of origin: Brazil

ORCID number: Amanda Meier 0000-0002-9856-5215; Kelser de Souza Kock 0000-0002-0117-6142.

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ORIGINAL ARTICLE

Observational Study

Critical care practices in the world: Results of the global intensive care unit need assessment survey 2020

Faisal A Nawaz, Neha Deo, Salim Surani, William Maynard, Martin L Gibbs, Rahul Kashyap

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Faisal A Nawaz, College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai 505055, United Arab Emirates

Neha Deo, Department of Medicine, Mayo Clinic Alix School of Medicine, Rochester, MN 55905, United States

Salim Surani, Rahul Kashyap, Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Salim Surani, Texas A&M University, College Station, TX 77843, United States

William Maynard, Rahul Kashyap, Internal Medicine, TriStar Centennial Medical Center, HCA Healthcare, Nashville, TN 37203, United States

Martin L Gibbs, Pulmonary and Critical Care, Tulane University School of Medicine, New Orleans, LA 70112, United States

Corresponding author: Salim Surani, FACP, FCCP, MD, MSc, Doctor, Professor, Critical Care Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, United States.
srsurani@hotmail.com

Abstract

BACKGROUND

There is variability in intensive care unit (ICU) resources and staffing worldwide. This may reflect variation in practice and outcomes across all health systems.

AIM

To improve research and quality improvement measures administrative leaders can create long-term strategies by understanding the nature of ICU practices on a global scale.

METHODS

The Global ICU Needs Assessment Research Group was formed on the basis of diversified skill sets. We aimed to survey sites regarding ICU type, availability of staffing, and adherence to critical care protocols. An international survey 'Global ICU Needs Assessment' was created using Google Forms, and this was distributed from February 17th, 2020 till September 23rd, 2020. The survey was shared with ICU providers in 34 countries. Various approaches to motivating healthcare providers were implemented in securing submissions, including use of

emails, phone calls, social media applications, and WhatsApp™. By completing this survey, providers gave their consent for research purposes. This study was deemed eligible for category-2 Institutional Review Board exempt status.

RESULTS

There were a total 121 adult/adult-pediatrics ICU responses from 34 countries in 76 cities. A majority of the ICUs were mixed medical-surgical [92 (76%)]. 108 (89%) were adult-only ICUs. Total 36 respondents (29.8%) were 31-40 years of age, with 79 (65%) male and 41 (35%) female participants. 89 were consultants (74%). A total of 71 (59%) respondents reported having a 24-h in-house intensivist. A total of 87 (72%) ICUs were reported to have either a 2:1 or ≥ 2:1 patient/nurse ratio. About 44% of the ICUs were open and 76% were mixed type (medical-surgical). Protocols followed regularly by the ICUs included sepsis care (82%), ventilator-associated pneumonia (79%); nutrition (76%), deep vein thrombosis prophylaxis (84%), stress ulcer prophylaxis (84%), and glycemic control (89%).

CONCLUSION

Based on the findings of this international, multi-dimensional, needs-assessment survey, there is a need for increased recruitment and staffing in critical care facilities, along with improved patient-to-nurse ratios. Future research is warranted in this field with focus on implementing appropriate health standards, protocols and resources for optimal efficiency in critical care worldwide.

Key Words: Intensive care unit; Critical care; Global; Survey; Intensive care unit survey; Intensive care unit needs

Core Tip: Intensive care unit (ICU) practices are variable across the world. Most common admitting diagnoses for ICUs worldwide are similar to Western reporting in literature. We aimed to survey sites regarding ICU type, availability of staffing, and adherence to critical care protocols. There is variable protocol penetration for processes of care in ICUs. Future research is warranted in this field with focus on implementing appropriate health standards, protocols and resources for optimal efficiency in critical care worldwide.

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INTRODUCTION

Critical care is defined by varying practices across countries worldwide. This is affected by multi-factorial trends in epidemiology, finance, and cultural and human resources that in turn influence patient outcomes[1].

Intensive care units (ICUs) are at the center of diverse practices in health systems around the world. Their needs are dictated by hierarchical arrangements, resource designation, patient demographics, and health practices, including the allied goals of health providers[2]. With a necessity for standardization deemed essential for efficiency and high-quality patient care, it is vital to understand the context of epidemiological variability, resource accessibility, and local health practices[3] in such sophisticated settings. Moreover, the current understanding and comparison of clinical practices, guidelines, equipment, and facilities available in different countries can help identify potential areas of quality improvement *via* protocol development and enhancement of unified care delivery. Current literature on this topic can be found in developed countries[4,5]; however, it is significantly limited in multinational settings[6-8] on a global level.

We aimed to delineate the critical care practices that are found worldwide and their characteristics, including staffing, ICU resources, and adherence to protocols. This study sets a novel benchmark in sharing insights on key areas of critical care by highlighting the state of ICUs across different countries and understanding the trends in contemporary health systems. By defining gaps in knowledge, resources, and protocols, this study can facilitate the development of best practice strategies and thereby

lay a strong foundation for critical care provision worldwide[9].

MATERIALS AND METHODS

Study design

This was a cross-sectional, multinational, survey-based study. We proposed the formation of a multidisciplinary, diverse team of skilled researchers who established the "Global ICU Needs Assessment Research Group".

A questionnaire was developed under the guidance of this research group with the goal of evaluating most common patient presentations, and resource needs in terms of ICU equipment and assisting technology.

Study variables

Furthermore, we asked about other variables, such as the availability of intensivists, residents, fellows, 12-h in-house intensivists, and patient/nurse ratio, along with other demographics of those surveyed, such as their level of qualification, duration of clinical experience, and overall expertise in this field. It was also deemed crucial to include outcome variables, such as mechanical ventilation (MV) duration, MV mortality, ICU length of stay, ICU mortality, and sepsis mortality as well. Using a pilot study approach, we implemented this strategy within a randomized group of ICU clinicians before proceeding with the main study phase. This was done for internal validation purposes in the form of a survey shown in the digital supplement.

Sample of convenience was done. Intensivists were contacted using social media platforms and personal networking and *via* critical care societies. The survey was designed using Google™ forms online and sent out from February 17th, 2020 to 23rd September, 2020, to critical care professionals in 34 countries worldwide (Figure 1). The need for regular follow-ups and motivation within critical care professionals was a vital factor to this study. This was achieved by leveraging various online platforms, such as e-mail and social media applications including WhatsApp™[20].

Using a diverse set of researchers, critical care physicians, and digital platforms, a sample of 122 ICUs was acquired through this questionnaire.

Statistical analyses

The responses were presented as stratified data in the form of mean, with standard deviation, or median with interquartile range. It was also deemed necessary to include relevant pictographic presentation of this data.

Descriptive statistical analysis was used after obtaining eligibility for category-2 Institutional Review Board exempt status.

ICU practices at a given healthcare facility, including details about the respondents and demographics of the facility. The survey asked about the state of the ICU being open or closed, type of patients receiving care, number of ICU beds, protocols implemented for efficient practice.

RESULTS

The respondents of this survey primarily reflected a young adult population, with the respondents of this survey primarily reflected a young adult population with the greatest proportion 31-40 years old and males representing the majority, n = 79 (65%) with an average ICU experience of 3 years. Moreover, consultants were the main constituents of the survey respondents at n = 89 (74%), followed by residents from post-graduate year 3 and above (18, 15%). The ICU settings were mostly designed as a mixed medical-surgical environment (92, 76%) in academic teaching hospitals (38, 32%) with an average of 16 (interquartile range 11-20) beds. Furthermore, the ICUs were commonly open type, (53, 44%) (Table 1).

The need for intensivists and nurses to lead critical care is noted worldwide[1]. The analysis showed a patient/nurse ratio of 2:1 being implemented in the majority (55%) of the ICU units, and only (10%) of responders were following a 1:1 nursing care approach. Moreover, 34% of ICUs, which typically functioned at 2:1 patient/nurse ratios, transferred to 1:1 for complicated cases. There was also a significant number of ICUs (20, 16.5%) working with more than a 2:1 patient/nurse ratio. It is also noteworthy that a vast majority of the ICUs (101, 84%) were led by certified intensivists with 24-h intensivists deployed in 71 (59%) of the ICUs for optimal patient care. Other notable providers were residents/fellows/medical students active in 101 (84%) ICU units (Table 2).

Critical care was driven by protocols that were followed within all ICU facilities. There was a strong predominance of protocols for Advanced Cardiac Life Support (93%), glucose control (89%), stress ulcer prophylaxis (84%), deep vein thrombosis (DVT) prophylaxis (84%) and sepsis care (82%). The protocols least reported included palliative care/end of life (44%), acute lung injury (55%), transfusion restriction (59%), hypothermia after cardiac arrest (61%), and delirium (67%) (Table 3).

Table 1 Demographic variables

Demographic variables	Responses in % (*n* = 121)
Age (yr)	
31-40	29.8
41-50	23.1
20-30	23.1
> 50	24.0
Gender	
Male	65.3
Female	34.7
Intensive care unit experience (yr)	
< 10	50.4
10-20	35.5
21-30	9.9
> 30	4.1
Designation	
Consultant staff	73.6
Resident-PGY-3 and above	14.9
Resident-PGY-1	5.0
Resident-PGY-2	6.6
Intensive care unit specialty wise distribution	
Mixed medical-surgical	76.0
Medical	7.4
Others	16.6
Institution type	
Private/non-academic	16.5
Government hospital (tertiary care)	19.8
Academic teaching hospital	31.5
Corporate teaching hospital	8.2
Other	0.9
Number of intensive care unit beds	
< 11	28.1
11-20	31.4
21-30	23.1
> 30	17.4
Intensive care unit type	
Open	43.8
Closed	56.2

PGY-3: Post-graduate year 3.

The sample population was analyzed across a total 121 adult/adult-pediatrics ICU responses from 34 countries in 76 cities. Distribution of the respondents was spread amongst North America (41.3%), Asia (30.5%), Europe (18.2%), Africa (5.8%), South Africa (2.6%) and Oceania (1.6%) (Figure 1).

Table 2 Clinical resource parameters

Clinical resource parameters	Responses in % (*n* = 121)
Patient/nurse ratio (*n*)	
Usually 2:1 (for complicated patients 1:1) (*n* = 41)	33.9
2:1 (*n* = 26)	21.5
> 2:1 (*n* = 20)	16.5
1:1 (*n* = 31)	25.6
No fixed patient/nurse (*n* = 3)	2.5
24 h in-house intensivist (*n* = 71)	58.7
Certified intensivist (*n* = 101)	83.5
Residents/fellows/medical students rotate through or cover intensive care units along with staff intensivists (*n* = 101)	83.5

Table 3 Critical care protocols self-reporting

High (%)		Medium (%)		Low (%)	
Glucose control	89.3	Daily interruption of sedation	69.4	Palliative care/end of Life	43.8
Advanced cardiac life support	93.4	Acute coronary syndrome	81.0	Delirium	66.9
Deep vein thrombosis prophylaxis	83.5	Acute lung injury	54.5	Early mobility	68.6
Stress ulcer prophylaxis	83.5	Transfusion restriction	58.7	Hypothermia after cardiac arrest	61.2
Severe sepsis	81.7				
Ventilator-associated pneumonia bundle	78.5				
Nutrition	76.0				

The most common diagnoses for patients admitted into the ICU settings in this study included sepsis (88%), respiratory failure (88%) and heart failure (55%), as shown in Table 4.

The average ICU mortality (*n* = 36) assessed in this survey was 14% (interquartile range 2-40); ICU length of stay (*n* = 41) was 5.2 d (interquartile range 2-21); mechanical ventilation (MV) duration (*n* = 34) was 4.3 d (1-15); MV patient mortality (*n* = 27) was 20% (1-64) and sepsis mortality (*n* = 27) was at 21% (5-70) across the survey respondents (Table 5).

DISCUSSION

In a multi-national study that evaluates the critical care practices of 121 ICUs in 34 countries, the majority of the centers were from mixed medical-surgical or medical practices, with consultants comprising the majority of respondents. The most common diagnoses included sepsis/septic shock and respiratory failure. The largest proportion of responders were young adult males who identified as intensivists, suggesting that this field is expanding to include more learners who are early in their training.

Considering that this was a multinational study, it is important to note that local practices and resources may vary between different regions. A lack of resources may limit the total number of beds available, or even result in a lower number of monthly admissions[10] in a given center relative to other regions. Because financial resources may influence how patients are triaged or how the healthcare organization is structured[11], it is important to keep this in mind when evaluating multi-center data from different countries.

The predominant diagnosis in the ICU was sepsis. Studies show that sepsis has a mortality rate varying from 13% to 39%[12]. The second most common diagnosis was respiratory failure, with studies indicating a mortality rate of 26.2%[13]. Both sepsis and respiratory failure followed the same trend that is observed in country-specific ICU studies[14]. Considering that the mortality rates of both diseases are so high, it is imperative that ICUs are equipped with the resources and training to achieve best practice guidelines[15].

Many of the reported surveys were from individuals in mixed medical-surgical ICUs that were closed in nature and had 24-h intensivists. Additionally, the greatest number of the respondents reported

Table 4 Common diagnoses

Common diagnoses	No	% of intensive care unit
Sepsis or septic shock	106	87.6
Respiratory failure	106	87.6
Heart failure	67	55.4
Post-operative observation	68	56.2
Poisoning	15	12.4
Head trauma	37	30.6
Renal failure	46	38.0
Alcohol withdrawal	13	10.7
Epilepsy or uncontrolled seizures	18	14.9
Chronic obstructive pulmonary disease exacerbation	37	30.6
Hypertension	15	12.4
Cardiogenic shock	37	30.6
Electrolyte imbalance	20	16.5
Hypotension or hypovolemic shock	44	36.4
Heat stroke	4	3.3

Table 5 Critical care outcomes

Variables	Outcome
Intensive care unit mortality (response n =36)	14%
Intensive care unit length of stay, in days (response n = 41)	5.2
Mechanical ventilation mortality (response n = 27)	19.5%
Mechanical ventilation duration, in days (response n = 34)	4.3
Sepsis mortality (response n = 27)	21.2%

having 11-20 beds in the ward. Most of these centers were within academic or privately-owned hospitals. Although it is believed that ICUs with more beds will achieve better optimal care, it is important to consider that more money shifted towards ICUs will limit funding to other departments [16]. This predominantly impacts areas of low-resource settings, which is why the median ICU beds in low-income countries is 8[7]. Closed ICUs are associated with better outcomes, such as shorter ICU stay and decreased ICU costs[17]. North America is reported to have the lowest amount of closed ICUs (63%), with Western Europe having the highest (89%) (17). Since closed ICUs require an intensivist working on site, more and more ICUs are now including a 24-h intensivist, which can lead to decreased risk of in-hospital death and rate of complications[1].

Respondents most often reported a patient/nurse ratio of 2:1, which flexed to 1:1 for complicated patients. In a study by Sakr *et al*[1] it was reported that a patient/nurse ratio of more than 1.5:1 was associated with a higher risk of in-hospital death. Adequate care in ICUs requires proper staffing of nurses. This can greatly impact patient outcomes, especially if there are limited nurses available to provide care[1]. A high patient/nurse ratio can result in more mistakes being made due to a stressful work environment and fatigue[18]. It is imperative that adequate staffing is provided to ICUs to best provide patient care in an optimized environment.

Kredo *et al*[19] noted that evidence-informed best practice guidelines are imperative to optimizing patient care. A multifaceted, team-based approach in the ICU is the best way of reinforcing these guidelines and developing strategies that can better manage the patient or prevent complications[15]. In our survey, we found that a majority of centers are able to follow best practice guidelines related to glucose control, advanced cardiac life support, DVT prophylaxis, and stress ulcer prophylaxis. However, challenges exist with protocols related to palliative care, acute lung injury, and transfusion restriction. It is important to address barriers to guideline adherence, which can differ from region to region. Some commonly reported barriers include lack of knowledge[20] or needing effective leadership to promote adoption of guidelines[21].

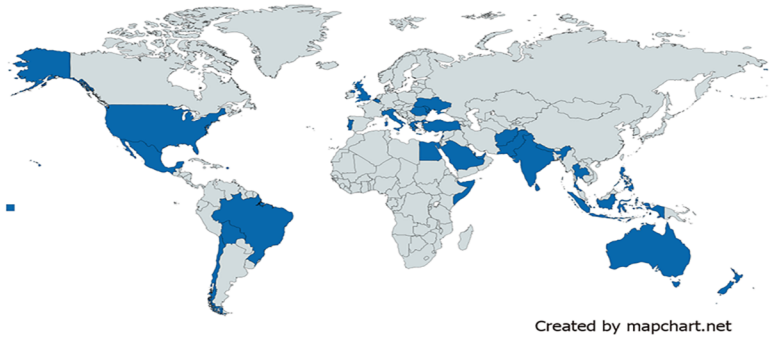

Figure 1 The survey was designed using Google™ forms online and sent out from February 17th, 2020 to 23rd September, 2020, to critical care professionals in 34 countries worldwide. Created by mapchart.net.

Strengths

The strengths of this study include being one of the first multinational surveys to collect data from 34 countries during the pandemic of the century[22]. Having more regions participate in a survey like this is beneficial because it provides a snapshot of the ICU statistics in that area. A multi-center design allows for a broader range of data representing the resources of each area *vs* a single center study. These data can be used to evaluate current ICU resources and limitations worldwide and can therefore help administration create designs to optimize care for patients who are in the critical care unit. Such multi-national collaborations would lead to robust data collection during pandemic and peace times[23-25].

Limitations

Our study has several limitations. First, since our primary recruitment method was through social media and networking at critical care societies, we may be missing out on data from remote areas or sites that did not see our recruitment invitation online. Second, as we had only 34 countries represented, a larger sample size from different geographical locations would allow us to understand the needs of the ICU in those regions better. Recall bias is also a factor in survey studies, as participants may not be able to fill in all the information as accurately as possible. Additionally, since this survey was filled out during the year of the coronavirus disease 2019 pandemic, ICUs may have been impacted or changed very drastically to meet the needs of their community. Therefore, the reported results may not accurately reflect ICU data prior to the pandemic. A final limitation to our study is that we did not stratify our data into geographical regions to evaluate differences from region to region. Further research could aim to delineate this data.

CONCLUSION

This international, multi-dimensional, needs-assessment survey reflects a need for increased recruitment and staffing in critical care facilities, along with improved patient-to-nurse ratios. Multi-center ICU data are imperative in designing future critical care delivery models that reflect the needs of the patient and address barriers to their care. Understanding current trends in health systems helps us develop quality improvement interventions that can lead to better outcomes in patients.

ARTICLE HIGHLIGHTS

Research background

There is variability in intensive care unit (ICU) resources and staffing worldwide. This may reflect variation in practice and outcomes across all health systems.

Research motivation

By understanding the nature of ICU practices on a global scale, administrative leaders can create long-term strategies for improved research and quality improvement measures.

Research objectives

We aimed to delineate the critical care practices that are found worldwide and their characteristics, including staffing, ICU resources, and adherence to protocols.

Research methods

An international survey 'Global ICU Needs Assessment 2020' was created using Google Forms, and this was distributed from February 17th, 2020 till September 23rd, 2020. The survey was shared with ICU providers in 34 countries.

Research results

There were a total 121 adult/adult-pediatrics ICU responses from 34 countries in 76 cities. A majority of the ICUs were mixed medical-surgical (92, 76%). 108 (89%) were adult-only ICUs. Total 36 respondents (29.8%) were 31-40 years of age, with 79 (65%) male and 41 (35%) female participants. 89 were consultants (74%). A total of 71 (59%) respondents reported having a 24-h in-house intensivist.

Research conclusions

Based on the findings of this international, multi-dimensional, needs-assessment survey, there is a need for increased recruitment and staffing in critical care facilities, along with improved patient-to-nurse ratios.

Research perspectives

Future research is warranted in this field with focus on implementing appropriate health standards, protocols and resources for optimal efficiency in critical care worldwide.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Faisal A Nawaz 0000-0002-0701-7628; Neha Deo 0000-0002-0583-8916; Salim Surani 0000-0001-7105-4266; William Maynard 0000-0002-0958-4183; Martin L Gibbs 0000-0003-1689-0012; Rahul Kashyap 0000-0002-4383-3411.

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META-ANALYSIS

Diuretic combinations in critically ill patients with respiratory failure: A systematic review and meta-analysis

Jean Maxime Côté, Nadir Goulamhoussen, Blaithin A McMahon, Patrick T Murray

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Jean Maxime Côté, Nadir Goulamhoussen, Division of Nephrology, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montréal H2X0C1, Québec, Canada

Blaithin A McMahon, Division of Nephrology, Department of Medicine, Medical University of South Carolina, Charleston, SC 29425, United States

Patrick T Murray, Department of Medicine, School of Medicine, University College Dublin, Dublin D078NN, Ireland

Corresponding author: Jean Maxime Côté, FRCP (C), MD, MSc, Consultant Physician, Division of Nephrology, Department of Medicine, Centre Hospitalier de l'Université de Montré al, CHUM 1000 St Denis, Montréal H2X0C1, Québec, Canada.
jean-maxime.cote@umontreal.ca

Abstract

BACKGROUND

In patients with respiratory failure, loop diuretics remain the cornerstone of the treatment to maintain fluid balance, but resistance is common.

AIM

To determine the efficacy and safety of common diuretic combinations in critically ill patients with respiratory failure.

METHODS

We searched MEDLINE, Embase, Cochrane Library and PROSPERO for studies reporting the effects of a combination of a loop diuretic with another class of diuretic. A meta-analysis using mean differences (MD) with 95% confidence interval (CI) was performed for the 24-h fluid balance (primary outcome) and the 24-h urine output, while descriptive statistics were used for safety events.

RESULTS

Nine studies totalling 440 patients from a total of 6510 citations were included. When compared to loop diuretics alone, the addition of a second diuretic is associated with an improved negative fluid balance at 24 h [MD: -1.06 L (95%CI: -1.46; -0.65)], driven by the combination of a thiazide plus furosemide [MD: -1.25 L (95%CI: -1.68; -0.82)], while no difference was observed with the combination of a loop-diuretic plus acetazolamide [MD: -0.40 L (95%CI: -0.96; 0.16)] or spironolactone [MD: -0.65 L (95%CI: -1.66; 0.36)]. Heterogeneity was high and the report of clinical and safety endpoints varied across studies.

CONCLUSION
Based on limited evidence, the addition of a second diuretic to a loop diuretic may promote diuresis and negative fluid balance in patients with respiratory failure, but only when using a thiazide. Further larger trials to evaluate the safety and efficacy of such interventions in patients with respiratory failure are required.

Key Words: Respiratory failure; Diuretics; Fluid management; Furosemide; Thiazide; Systematic review

Core Tip: Loop diuretics are a cornerstone treatment to maintain fluid balance in patients with respiratory failure, but resistance is common. In the caveat of a substantial heterogeneity, this meta-analysis shows a significant increase in urine output with negative fluid balance with the combination of loop diuretics plus thiazides compared to loop diuretics alone in patients with respiratory failure. Further trials are required to confirm the safety and efficacy of such interventions in patients with respiratory failure.

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INTRODUCTION

Progressive fluid accumulation is a commonly encountered scenario in critically ill patients and in patients with acute kidney injury (AKI), acute heart failure, and other edematous states. Fluid overload is associated with increased mortality[1,2] and numerous systemic complications such as poor wound healing, AKI and pulmonary edema with acute hypoxemic respiratory failure (AHRF)[3]. Interpretation of studies evaluating the relationship between fluid balance and mortality in AHRF is complex, especially in the context of other organ outcomes[4]. Early observational studies of fluid management in the specific context of patients with AHRF have shown that a negative fluid balance is associated with improved survival, particularly in the context of acute respiratory distress syndrome (ARDS)[5,6]. Though, the definitive trial evaluating fluid management during ARDS showed that a conservative fluid balance achieved with diuretics did not statistically affect mortality but did increase the number of ventilator-free days and intensive care unit (ICU)-free days survival[7].

In the ICU, loop diuretics remain the most widely used class of diuretics, and are used in up to 49% of all ICU admissions[8]. However, prolonged use of loop diuretics may be associated with therapeutic resistance, which is a frequent observation in the ICU and associated with increased risk of mortality[9]. Combining multiple diuretics with different mechanisms of action may achieve a sequential nephron blockade, further limiting the kidney's ability to reabsorb fluid and electrolytes. These actions may further increase urine output, but also potentially lead to complications such as electrolyte and acid-base disorders and worsening kidney function[10,11]. Diuretic combinations are routinely used in the management of heart failure, and there is a significant body of evidence supporting that practice[12,13]. Both American and European Heart Failure Guidelines recommend that when diuresis remains inadequate with loop diuretic therapy despite dose escalation, the addition of thiazide diuretics may be considered[14,15]. Recent data have also shown that the addition of a second diuretic can help to mitigate loop-diuretic resistance in a broad cohort of patients hospitalised in the ICU[16].

However, in patients with AHRF, only few data exist on the additional efficacy of various diuretic regimens to promote diuresis in resistant edematous states, despite the use of this approach in up to 6% of all ICU admissions[8]. Instead of progressively escalate the dose in patients resistant to loop diuretics, a proactive administration of a second diuretic may help to quickly increase the urine output, and therefore minimize respiratory complications. On the other hand, as opposed to patients with heart failure where the extravascular fluid retention usually represents multiple liters, patients with AHRF may have a relatively small fluid retention but enough to significantly affect the perturbed pulmonary physiology. In these patients, the risks of quickly increasing the diuresis, and therefore having a substantial negative fluid balance, may be higher regarding renal function, electrolyte homeostasis or hypotension. To date, no systematic review has evaluated different protocols of diuretic combinations in this population regarding their efficacy but also their safety.

Scope

The aim of this systematic review was to determine the efficacy of common diuretic combinations to promote negative fluid balance in patients hospitalised in the ICU with AHRF. The objective was to compare the use of loop diuretics in monotherapy to the use of a loop diuretic with an adjunctive non-loop diuretic agent paying particular attention to rates of AKI and electrolyte disturbance.

MATERIALS AND METHODS

This systematic review with meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines[17]. The protocol was registered on the PROSPERO international prospective register of systematic reviews (CRD42020218381).

Eligibility criteria

Inclusion criteria: Eligible studies compared diuretic combinations to loop diuretics alone in adult patients hospitalised in ICU with respiratory failure receiving diuretics for volume control. Respiratory failure was defined as receiving invasive or non-invasive positive ventilation for an acute hypoxemic or hypercapnic respiratory failure, or for severe pulmonary edema requiring oxygen therapy. Patients with non-primary pulmonary aetiology, such as acute decompensated heart failure, were included if signs of severe pulmonary edema requiring oxygen, with or without mechanical ventilation, were clearly reported. Studies evaluating a combination of diuretic agents without a comparison group were included in the systematic review if at least one efficacy clinical outcome of interest was reported, but were not included in the final meta-analysis. The following classes of non-loop diuretics in combination with a loop diuretic were included: Thiazide or thiazide-like agents, carbonic anhydrase inhibitors, Epithelial sodium channel (ENaC) inhibitors and mineralocorticoid antagonists. No study design, date or language limits were imposed on the literature search, although only studies in English, Spanish and French were included in the analysis.

Exclusion criteria: Studies reporting patients with peripheral edema only were excluded. Studies reporting patients with chronic kidney disease (CKD) treated with maintenance kidney replacement therapy (KRT) were also excluded. Studies of the use of loop diuretic agents in pediatric populations were excluded.

Literature search

According to the predetermined protocol, a systematic literature search of 4 databases (MEDLINE, Embase, Cochrane Library and PROSPERO) was performed from inception until May 5, 2021 in collaboration with a trained medical librarian (covering from 1946 to May 2021). The literature search strategy was developed using medical subject headings and text words related to all classes of diuretics included and their individual name, fluid balance, respiratory failure and hypoxemia, and critical care (Supplementary Table 1). We also scanned the reference lists of included studies and searched the grey literature for all abstracts listed into the annual meeting archives of the *American Society of Nephrology*, the *European Society of Intensive Care Medicine* and the *Society of Critical Care Medicine*. Finally, a bibliography of all potentially included articles was circulated to all authors, to prompt consideration of any other relevant publications.

Study selection

Eligible studies were clinical trials, observational cohort studies, case-control studies and cross-sectional studies. Cases series with more than five patients and abstracts not yet published were also included when at least one outcome of interest was described quantitatively. Literature search results were uploaded and screened using *Rayyan QCRI* application. Two reviewers (JMC and NG) independently screened the titles and abstracts of all identified articles. These reviewers then screened the full-text reports for all potential studies and decided whether these met the inclusion criteria, reporting the reason(s) for exclusions. When necessary, the authors (JMC and BMcM) contacted the corresponding author of potential studies to obtain additional information. Once the final list of included articles was determined, there was no disagreements between authors.

Data extraction

RevMan (Version 5.4, The Cochrane Collaboration, 2020) was used to extract data from each eligible study. Data extracted included eligibility criteria, demographics, methodology, diuretic name, class and dosage, risk of bias and results. The prespecified primary efficacy outcome of interest was the cumulative fluid balance, and secondary outcomes were the 24-h urine output (diuresis), ventilation-free survival, number of days on mechanical ventilation, need of therapeutic paracentesis, hospital and ICU length-of-stay, in-hospital and 90-d mortality. Due to lack of data regarding the cumulative ICU fluid balance for all included studies, the 24-h fluid balance was therefore reported as primary outcome. Safety endpoints included AKI incidence and progression to KRT, electrolyte and acid-base

abnormalities, creatinine and electrolyte changes from baseline (sodium, potassium, bicarbonate) and, finally, hypotensive events, arrythmias and ototoxicity occurrence. Reports of 24-h natriuresis, not planned in the original protocol, were also captured as this endpoint was considered clinically relevant.

The risk of bias was assessed using the Cochrane Collaboration tool for assessing the risk of bias for randomised controlled trials (RCTs) (RoB2)[18], and non-randomised trials (n-RCTs)(ROBINS-I)[19], and the Newcastle-Ottawa Scale for observational studies. These assessments were based on the reporting of fluid balance, the primary outcome of the current review. When insufficient details were reported, the risk of bias was judged as unclear.

Statistical analysis

A meta-analysis using mean differences (MD) with 95% confidence interval (CI) was performed for the primary outcome and for the 24-h urine output (secondary efficacy endpoint), while descriptive statistics were used for all other endpoints reported. The statistical heterogeneity for pooled results was reported using I^2. As the clinical heterogeneity of included studies was considered high, a random-effects model was used for both meta-analyses. In studies reporting the endpoint using median and IQR, the statistical method described by Wan *et al*[20] was used to convert the reported value to mean ± SD allowing meta-analysis. None of the preplanned sub-analyses (dosage of loop diuretics and the type of respiratory failure) were performed due to limited data. All statistical analyses were performed on *RevMan* (Version 5.4, The Cochrane Collaboration, 2020) and SPSS (Version 26, IBM, Armonk NY).

RESULTS

Study selection

Study selection is depicted in Figure 1. After removal of duplicates, there were 6510 studies. Of these, 6476 were excluded after screening titles and abstracts. A total of 34 studies were assessed for eligibility, from which 25 were excluded for not meeting inclusion criteria (Supplementary Table 2). Therefore, a total of 9 studies were included[21-29], from which 8 presented quantitative results for endpoints meta-analysis[21-23,25-29].

Study characteristics

A detailed summary of each of the study characteristics is presented in Table 1. The included studies investigated the combination of furosemide with either spironolactone[21], indapamide[22], chlorothiazide[23,27,29], metolazone[23,27,28], acetazolamide[24,25] or a combination of hydrochlorothiazide and amiloride[26] at various doses in patients with respiratory failure. These studies were published between 1997 and 2019, and included a total of 440 participants. Three studies were RCTs[21,22,25] and 5 were observational[23,24,27-29], and one was a prospective non-randomised interventional study[26].

For the study by Heming *et al*[24], only 29 from the 68 participants were receiving a loop diuretic in addition to acetazolamide. All results reported from this study were calculated using the subset of the entire cohort receiving that combination of diuretics based on the dataset shared by the authors. Similarly, only patients with confirmed ICU admission with respiratory failure from the Shulenberger *et al*[29] study (n = 78, from 177 in total) were included in this review, after access to the original dataset. Overall, in this review, females were the minority and the median age ranged from 57 to 77 years. Most patients were admitted following cardiac surgery or acute decompensated heart failure. The duration of the diuretic combination intervention varied from 24 to 96 h, while the median furosemide dose (equivalent to intravenous furosemide) ranged from approximately 80 to 351 mg *per* day. The doses of the second diuretic are reported in Table 1.

Risk of bias

The quality assessment and risks of bias are presented in the Supplementary Material (Supplementary Table 3). All 3 RCTs included[21,22,25], despite limited sample size, were good quality with an overall low risk of bias. The non-randomised interventional trial was classified with an overall unclear risk of bias, due to missing data[26] and potential uncontrolled confounders. The observational cohort studies included were of good quality, where the risk of bias was adequately minimized for most components of the Newcastle-Ottawa Assessment Scale. No unpublished data was included in this review. Heterogeneity was substantial across all included studies, regarding study design, intervention duration and timing of administration, dose of loop-diuretics administered, baseline kidney function and safety endpoints reported. Notably, the intervention duration, defined as the period of diuretics administration during which clinical endpoints were measured, ranged between 24 h to 96 h. In addition, regarding the second diuretic, some studies reported a fixed dose for all patients, while other reported a titratable dose. The comparison group receiving only a loop-diuretic was an independent and parallel-group for 4 studies[21,22,25,26], and a sequential paired group–where clinical endpoints were compared before and after the addition of a second diuretic within the same group–for 4 studies[23,27-

Table 1 Characteristics of included studies

Ref.	Country, design	Inter-vention duration	Major eligibility criteria	Study groups (sample size)	Median daily dose of diuretic (route)	Patients characteristics	
Apte *et al*[21], 2008	Australia; RCT	72 h	(1) Mechanically ventilated; and (2) On continuous IV furosemide	Furosemide + Spironolactone (*n* = 10)	97 mg (71-288) (IV); 300 mg (PO)	(1) Age: 68 (55-79); (2) Male sex: 7 (70%); (3) SCr, μmol/L: -; (4) Apache II Score: 21 (15-28); and (5) Positive ventilation: 10 (100%)	ICU admission for (1) Sepsis: 4 (40%); (2) Cardiovascular: 2 (20%); and (3) COPD/Resp. failure: 2 (20%). In-hospital mortality: -
				Furosemide + Placebo (*n* = 10)	168 mg (74-295) (IV)	(1) Age: 67 (52-76); (2) Male sex: 6 (60%); (3) SCr, umol/L: -; (4) Apache II Score: 24 (17-26); and (5) Positive ventilation: 10 (100%)	ICU admission for (1) Sepsis: 6 (60%); (2) Cardiovascular: 1 (10%); and (3) COPD/Resp. failure: 0 (0%). In-hospital mortality: -
Bihari *et al* [22], 2016	Australia; RCT	24 h	(1) Fluid overload (> 10% ICU admission weight); and (2) No prior diuretic last 48 h	Furosemide (*n* = 20)	1 mg/kg (IV); Median weight: 78 kg	(1) Age: 75 (62-86); (2) Male sex: 12 (60%); (3) SCr, μmol/L: 97 (69-133); (4) Apache III Score: 68 ± 21; and (5) Positive ventilation: 14 (70%)	ICU admission for (1) Sepsis: 3 (15%); (2) Cardiovascular: 3 (15%); and (3) COPD/Resp. failure: 12 (60%). In-hospital mortality: 5 (25)
				Furosemide + Indapamide (*n* = 20)	1 mg/kg (IV); 5 mg (PO)	(1) Age: 70 (53-75); (2) Male sex: 14 (70%); (3) SCr, μmol/L: 91 (63-141); (4) Apache III Score: 74 (29); and (5) Positive ventilation: 10 (50%)	ICU admission for (1) Sepsis: 3 (15%); (2) Cardiovascular: 4 (20%); and (3) COPD/Resp. failure: 10 (50%). In-hospital mortality: 5 (25)
Bohn *et al*[27], 2019[1]	United States; Observa-tional (paired groups)	24 h	(1) ADHF with reduced ejection fraction; and (2) Not responding to furosemide monotherapy	Furosemide + Chlorothiazide (*n* = 34, from 108)[1]	≥ 80 mg (IV); 500 to 1000 mg (IV)	(1) Age: 64 (54-69); (2) Male sex: 74 (69%); (3) SCr, umol/L: 132 (90-187); (4) Apache II Score: 12 (9-15); and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 108 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: 21 (19)
				Furosemide (*n* = 34, from 108)[1]	≥ 80 mg (IV)	-	-
				Furosemide + Metolazone (*n* = 16, from 60)[1]	≥ 80 mg (IV); 5 to 10 mg (PO)	(1) Age: 63 (54-74); (2) Male sex: 41 (68%); (3) SCr, umol/L: 142 (102-188); (4) Apache II Score: 10 (7-14); and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 60 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: 1 (2)
				Furosemide (*n* = 16, from 60)[1]	≥ 80 mg (IV)	-	-
Heming *et al* [24], 2011	France; Observa-tional	24 h	(1) Mechanically ventilated; and (2) Acute respiratory failure	Furosemide + Acetazolamide (*n* = 29, from 68)[2]	80 mg (40-80) (IV); 500 to 1000 mg (PO)	(1) Age: 77 (73-83); (2) Male sex: 9 (31%); (3) SCr, umol/L: 66 (57-89); (4) Apache II Score: 25 (20-30); and (5) Positive ventilation: 29 (100%)	ICU admission for (1) Sepsis: 6 (21%); (2) Cardiovascular: 5 (17%); and (3) COPD/Resp. failure: 16 (55%). In-hospital mortality: 10 (34)
Imiela and Budaj[25], 2017	Poland; RCT	96 h	(1) ADHF not responding to furosemide; and (2) Significant pulmonary overload	Furosemide[3] + Acetazolamide (*n* = 10)	110 mg (± 73) (IV); 250 to 500 mg (PO)	(1) Age: 73 (± 8.6); (2) Male sex: 8 (80%); (3) SCr, μmol/L: 137 (± 42); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 10 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: -
				Furosemide[3] (*n* = 10)	152 mg (± 97) (IV)	(1) Age: 71 (± 14); (2) Male sex: 9 (90%); (3) SCr, umol/L: 141 (±	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 10 (100%);

						77); (4) Apache II Score: -; and (5) Positive ventilation: -	and (3) COPD/Resp. failure: -
Michaud and Mintus[23], 2017	United States; Observational (paired groups)	24 h	(1) Hospitalized at the ICU; and (2) Received IV furosemide + 2nd diuretics for severe fluid overload	Furosemide + Chlorothiazide (*n* = 58)	280 mg (40-720) (IV); 392 mg (± 225) (IV)	(1) Age: 61 (± 12); (2) Male sex: 35 (60%); (3) SCr, μmol/L: 124 (± 53); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: 4 (6.8%); (2) Cardiovascular: 25 (43%); and (3) COPD/Resp. failure: 15 (26%). In-hospital mortality: 11 (19)
				Furosemide (*n* = 58)	193 mg (20-710) (IV)	-	-
				Furosemide + Metolazone (*n* = 64)	240 mg (20-960) (IV); 6.8 mg (± 3.3) (PO)	(1) Age: 65 (± 14); (2) Male sex: 31 (48%); (3) SCr, μmol/L: 115 (± 44); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: 9 (14%); (2) Cardiovascular: 24 (38%); and (3) COPD/Resp. failure: 12 (19%). In-hospital mortality: 17 (27)
				Furosemide (*n* = 64)	130 mg (20-750) (IV)	-	-
Ng *et al*[28], 2013	United States; Observational (paired groups)	48 h	(1) Hospitalized at the ICCU; and (2) Failed to respond to intermittent furosemide	Furosemide + Metolazone (*n* = 42)	80 mg (80-160) (IV); 5 mg (2.5-10) (PO)	(1) Age: 57 (± 13); (2) Male sex: 22 (52%); (3) SCr, μmol/L: 148 (± 88); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 42 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: 0 (0)
				Furosemide (*n* = 42)	80 mg (0-160) (IV)	-	-
Shulenberger *et al*[29], 2016	United States; Observational (paired groups)	24 h	(1) ADHF with loop-diuretic resistance defined as > 160 mg/d of furosemide; and (2) Admitted in the ICU	Furosemide + Chlorothiazide (*n* = 40, from 88)[4]	346 mg (± 144) (IV); 508 mg (± 273) (IV)	(1) Age: 59 (± 12); (2) Male sex: 26 (65%); (3) SCr, μmol/L: -; (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 40 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: 3 (8.5)
				Furosemide (*n* = 40)[4]	351 mg (± 143) (IV)		
				Furosemide + Metolazone (*n* = 38, from 89)[4]	261 mg (± 111) (IV); 5.7 mg (± 2.5)	(1) Age: 57 (± 13); (2) Male sex: 19 (50%); (3) SCr, umol/L: -; (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 38 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: 9 (24%)
				Furosemide (*n* = 38)[4]	263 mg (± 102) (IV)		
Vánky *et al* [26], 1997	Sweden; n-RCT (unpaired groups)	24 h	(1) Hospitalized at the ICU post-Cardiac surgery; and (2) Received IV furosemide for severe fluid overload	Furosemide + HCTZ + Amiloride (*n* = 20)	87 mg (± 4) (IV); 50 mg (PO); 5 mg (PO)	(1) Age: 70 (± 1.4); (2) Male sex: 15 (75%); (3) SCr, μmol/L: 98 (± 3); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 20 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: -
				Furosemide (*n* = 57)	117 mg (± 18) (IV)	(1) Age: 67 (± 1.2); (2) Male sex: 40 (70%); (3) SCr, μmol/L: 105 (± 4); (4) Apache II Score: -; and (5) Positive ventilation: -	ICU admission for (1) Sepsis: -; (2) Cardiovascular: 57 (100%); and (3) COPD/Resp. failure: -. In-hospital mortality: -

[1]Bohn *et al*[27]: Baseline characteristics reported are from the whole cohort. However, only critically ill patients receiving vasopressors (Chlorothiazide: 34, Metolazone: 16) were included in aggregated data.

[2]Heming *et al*[24]: Only 29 participants from the whole cohort (*n* = 68) received a loop-diuretic in combination with acetazolamide. All aggregated data were re-analysed using the original dataset shared by the authors.

[3]Some patients received torsemide. The dose was converted to furosemide equivalent.

[4]Shulenberger *et al*[29]: Only intensive care unit patients (Chlorothiazide: 40, Metolazone: 38) were included in aggregated data, after re-analysis based on the original dataset shared by the authors.

RCT: Randomized Controlled Trial; ADHF: Acute decompensated heart failure; SCr: Baseline Serum creatinine; ICU: Intensive care unit; ICCU: Intensive cardiac care unit.

29].

Primary endpoint: Daily fluid balance

When combining all studies using various combinations of non-loop-diuretic plus loop-diuretic compared to loop-diuretics alone, a significant difference was observed in the primary outcome, with a MD in the 24-h fluid balance in favour of the combination group [overall MD: -1.06 L (95%CI: -1.46; -0.65), I^2 = 68%] (Figure 2A). However, when each combination diuretic class was analyzed separately, no significant difference was observed for the spironolactone-furosemide [MD: -0.65 L (95%CI: -1.66; 0.36), I^2 = NA] or the acetazolamide-furosemide combination [MD: -0.40 L (95%CI: -0.96; 0.16), I^2 = NA]. Thus, the observed effect on the daily fluid balance was mainly driven by the thiazide-furosemide combinations [MD: -1.25 L (95%CI: -1.68; -0.82), I^2 = 60%]. Inspection of the funnel plot (Supplementary Figure 1) showed no substantial publication bias toward specific studies.

Secondary efficacy endpoints

Similar findings were reported for the 24-h urine output, where the addition of a second diuretic was associated with an increase in the urine output by 1.08 L (95%CI: 0.65; 1.52, I^2 = 73%). Once again, that effect was mainly attributed to the thiazide-furosemide combination [MD: 1.30 L (95%CI: 0.81-1.79), I^2 = 76%] as no difference was observed for other combinations (Figure 2B). Overall, while the addition of spironolactone or acetazolamide to furosemide had a limited effect on fluid and sodium balance (Supplementary Table 4), the addition of a thiazide was associated with an increase in urine output by 14% for indapamide, 31% for hydrochlorothiazide plus amiloride, ranged from 52%-101% for metolazone and, finally, from 89%-114% for chlorothiazide, with corresponding effects on the negative fluid balance. In-hospital mortality, ICU length-of-stay, and hospital length-of-stay are depicted in Supplementary Table 5. Due to limited data, no pooled analysis was performed for these outcomes. No study reported the 28-d or 90-d mortality, need of therapeutic paracentesis and ventilation free-survival.

Safety endpoints

Available data on the physiological effects of these diuretic combinations on electrolytes and serum creatinine is shown in Table 2, but reporting was inconsistent. Due to significant heterogeneity across these studies, results for these endpoints were not pooled, but instead reported separately. No diuretic combination was associated with a substantial serum creatinine change at 24-h from baseline. According to the specific segment of the nephron targeted, varied impacts on electrolytes were observed for these three diuretic classes; for example, whereas a limited increase in serum potassium was observed with the spironolactone combination, a decrease in serum potassium was observed in all thiazide studies reporting this endpoint. Notably, as opposed to thiazide and loop-diuretic combinations, with which an increased in serum bicarbonate was observed, treatment with acetazolamide for 24-h reduced serum bicarbonate levels by 3.6 ± 5.1 mmol/L.

The risk of all other adverse (safety) events, where definitions and follow-up varied across included studies, are reported in Supplementary Table 6. Notably, hypokalemia was documented in 6 studies and ranged from 0% to 85%, while hyponatremia was documented in 4 studies and ranged from 0% to 43% when combining a thiazide with a loop-diuretic. No study reported arrythmia or ototoxicity events.

DISCUSSION

To our knowledge, this is the most comprehensive systematic review and meta-analysis to address the clinical efficacy and safety of various diuretic combinations in the context of patients hospitalised at the ICU with fluid overload and respiratory failure. A significant increase in the 24-h urine output leading to a negative fluid balance was observed in the pooled analyses, mainly attributed to the thiazide-furosemide combination. Reporting of other clinical endpoints including the efficacy, safety, and clinical outcomes of groups treated with each combination was inconsistent and generally incomplete.

Currently, strategies to manage fluid balance in critically ill patients with acute lung injury and other causes of respiratory failure include fluid restriction but this may be difficult given the requirement of fluid for carriers for vasopressors, antibiotics, and nutrition. A preferred option is augmenting urine output with diuretics. In addition, positive sodium balance specifically, rather than simple fluid balance, has recently been associated with respiratory dysfunction in mechanically ventilated patients[30,31], and with worsening prognosis in decompensated heart failure[32]. Ensuring adequate negative sodium balance along with increased urine output may be crucial to optimising extracellular fluid volume and outcomes. This approach is now endorsed by the European Society of Cardiology[33]. Also, as recently confirmed by the STARRT-AKI trial, delaying initiation of KRT based on a watchful waiting approach (in the absence of emergency indications for RRT initiation) can be beneficial by reducing RRT complications including prolonged KRT requirement[34]. Therefore, refining the ways to achieve a negative fluid balance with a diuretic combination strategy might potentially delay or avoid the need for RRT initiation (including ultrafiltration) to treat volume overload and control fluid balance in patients with loop-diuretic resistance.

Table 2 Safety events and change in serum creatinine and electrolytes at 24-h for all included studies

Ref.	Treatment group	24-h biochemical changes[1]				Safety events, *n* (%)	
		Creatinine, μmol/L	Sodium, mmol/L	Potassium, mmol/L	Bicarbonate, mmol/L	Hyponatremia	Hypokalemia
Mineralocortocoid-antagonist							
Apte *et al*[21], 2008	Spironolactone + Furosemide (*n* = 10)	+4.8 (4.1-6.9)	-1.0 (?)	+0.13 (?)	-	-	-
	Furosemide (*n* = 10)	+23 (-4.4-39)	+3.0 (?)	+0.13 (?)	-	-	-
Thiazides							
Bihari *et al*[22], 2016	Indapamide + Furosemide (*n* = 20)	-5.2 ± 38	0 ± 0	-0.4 ± 1.8	+1.4 ± 6.3	0 (0)	0 (0)
	Furosemide (*n* = 20)	-2.3 ± 14	+2.0 ± 4.0	-0.2 ± 0.6	+0.9 ± 2.5	0 (0)	0 (0)
Bohn *et al*[27], 2019	CTZ + Furosemide (*n* = 34)	-	-	-	-	-	8 (24)
	MTZ + Furosemide (*n* = 16)	-	-	-	-	-	3 (19)
Michaud and Mintus [23], 2017	CTZ + Furosemide (*n* = 58)	-18 ± 57	+0.5 ± 5.6	-0.4 ± 0.6	+3.3 ± 5.1	15 (26)	10 (17)
	MTZ + Furosemide (*n* = 64)	-18 ± 73	-1.2 ± 5.3	-0.3 ± 0.6	+2.6 ± 5.6	25 (39)	11 (17)
Ng *et al*[28], 2013	MTZ + Furosemide (*n* = 42)	+2.7 ± 28	-	-	-	18 (43)	15 (35)
Shulenberger *et al* [29], 2016	CTZ + Furosemide (*n* = 40)	+8.8 ± 27	+0.1 ± 2.3	-	-	2 (5)[2]	34 (85)[3]
	MTZ + Furosemide (*n* = 38)	+18 ± 35	-0.7 ± 3.1	-	-	2 (5)[2]	27 (71)[3]
Vánky *et al*[26], 1997	HCTZ + Amiloride + Furosemide (*n* = 20)	-2.0 ± 7.1	-	-	-	-	-
	Furosemide (*n* = 57)	-2.0 ± 7.6	-	-	-	-	-
Carbonic anhydrase inhibitor							
Heming *et al*[24], 2011	Acetazo + Furosemide (*n* = 29)	+4.3 ± 9.4	-	-0.3 ± 0.4	-3.6 ± 5.1	-	9 (31)
Imiela and Budaj [25], 2017	Acetazo + Furosemide (*n* = 10)	-	-	-	-	-	-
	Furosemide (*n* = 10)	-	-	-	-	-	-

[1]Results are presented in median (IQR), or mean ± SD change within 24-h, from baseline.
[2]Only severe hyponatremia event (Na^+ < 125 mmol/L) were reported.
[3]Hypokalemia was defined as K^+ < 4.0 mmol/L, instead of 3.5 mmol/L for all other studies.
CTZ: Chlorothiazide; MTZ: Metolazone; HCTZ: Hydrochlorothiazide; Acetazo: Acetazolamide.

The mechanisms of resistance to furosemide and other loop diuretics is multifactorial[35]. They include a decrease in sodium delivery to the site of action by systemic and renal hypoperfusion[36], as well as an increase in sodium and water retention due to neurohormonal, renin-angiotensin-aldosterone and antidiuretic hormone systems activation in critically ill patients. In addition, proximal tubular injury or loss in AKI or CKD results in diminished loop diuretic secretion into the tubular lumen and reduced effects more distally in the thick ascending limb of Henle's loop, while in chronic exposure to furosemide, adaptive changes in the nephron occur with hypertrophy of the distal tubule leading to an increase of its reabsorptive capacity[37]. For patients who do not respond to an increasing dose of furosemide, sequential nephron blockade of sodium reabsorption with other classes of diuretics can overcome these resistance mechanisms[16], which was confirmed in the current review focusing on patients with AHRF.

In order to promote liberation from mechanical ventilation in patients with metabolic alkalosis and associated hypoventilation, normalisation of the acid-base state while improving fluid balance with acetazolamide has also been investigated[38-40]. Also, the combination of an aldosterone receptor antagonist with furosemide is recommended as first line therapy in cirrhotic patients with ascites[41], due to the efficacy of that combination to promote natriuresis while minimising the risk of hypokalemia. This combination is also widely recommended in the management of patients with chronic heart failure and has been shown to reduce morbidity and mortality in patients with reduced ejection fraction[42].

In this review, various factors may explain the limited efficacy of these combinations to promote diuresis and a negative fluid balance in some included studies. First, the dose of furosemide was not

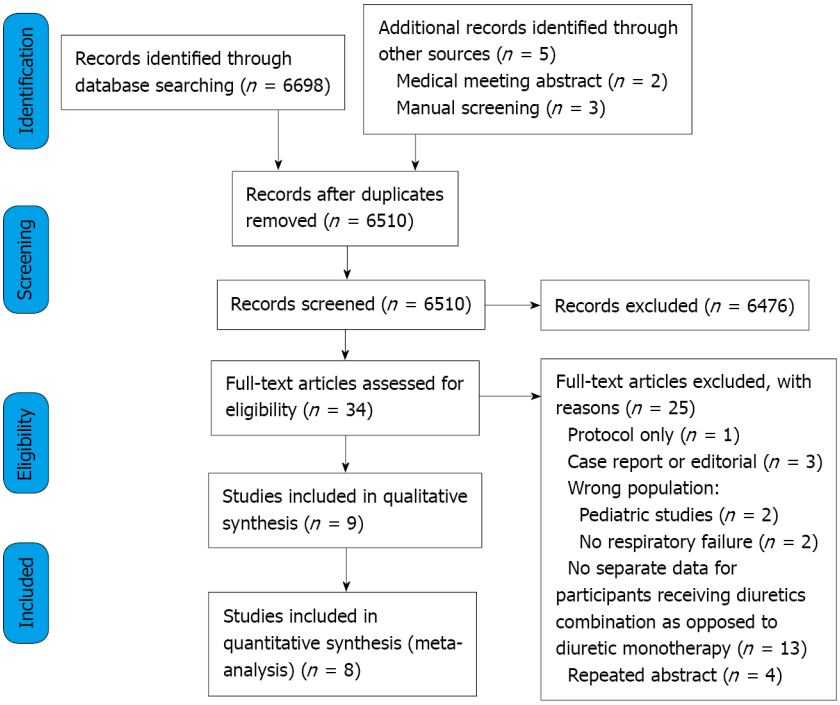

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Figure 1 Flow chart of included studies.

maximised for most studies, unlike recent RCTs on acute heart failure[12]. Indeed, the studies with higher median daily doses of furosemide were associated with higher and significant increases in urine output, even before addition of the second diuretic[23,29], which was also confirmed in previous cohorts[16]. On the other hand, the use of sub-maximal doses of multiple drugs in combination may additively or synergistically augment efficacy, while avoiding the adverse effects of higher doses of these drugs. Secondly, in the context of respiratory failure, the total negative fluid balance required to improve respiratory parameters may be less than the diuresis desired in patients with acute heart failure, in which the cumulative volume overload is usually greater[1]. As this review focused on the net fluid balance achieved instead of respiratory outcomes, it is still possible that the limited diuresis observed for these patients was judged as clinically sufficient to maintain an even fluid balance (rather than targeting negative fluid balance), as opposed to a fluid-liberal approach[7]. Also, none of these studies reported the use of an integrated tool, such as point-of-care ultrasound, bioimpedance, or other hemodynamic and volume measures[3], to evaluate the volume status of these patients, once again limiting the capacity to determine if the urine output achieved was adequate to optimise volume status.

All diuretic agents have a safety profile that varies according to their intrinsic mechanism of action. This review showed that combination of acetazolamide and furosemide may reduce serum bicarbonate and induce potassium loss, causing hypokalemia in up to 31% of patients[24] after only 24 h of treatment. In contrast, when furosemide is combined with thiazides, a trend toward an increase in bicarbonate and lower potassium levels was observed, reflecting the greater natriuretic and kaliuretic effects of reabsorption blockade in sequential nephron segments. The rate of hypokalemia was considerable, emphasizing the need to regularly monitor electrolyte levels, acid-base parameters, and kidney function (which is under-reported in this literature) when choosing such combinations. The role of potassium-sparing diuretics in the prevention of hypokalemia with aggressive diuretic regimens warrants further research.

In sum, this study brings new data on the use of diuretic combinations in the subgroup of ICU patients with AHRF, which has never been systematically reported before. The pooled analysis confirmed an increased efficacy regarding urine output and net fluid balance, which is interesting in a clinical setting, but also brings relevant data on the potential risk of substantial electrolyte disturbances in patients exposed to these combinations. Indeed, the study also confirms the need for additional lab monitoring when prescribing such combinations especially if no pre-emptive electrolytes administration is planned.

There are several limitations to the current systematic review. First, no study reported the pre-planned endpoint of cumulative fluid balance, which required us to deviate from the original protocol and to use the daily fluid balance as primary outcome. Also, no study reported the use of ENaC inhibitors alone (*e.g.* triamterene, amiloride) in conjunction with furosemide, which did not allow this review to evaluate that combination. This highlights the importance of future studies using ENaC inhibitors in combination with loop-diuretics in the management of respiratory failure. In addition, the

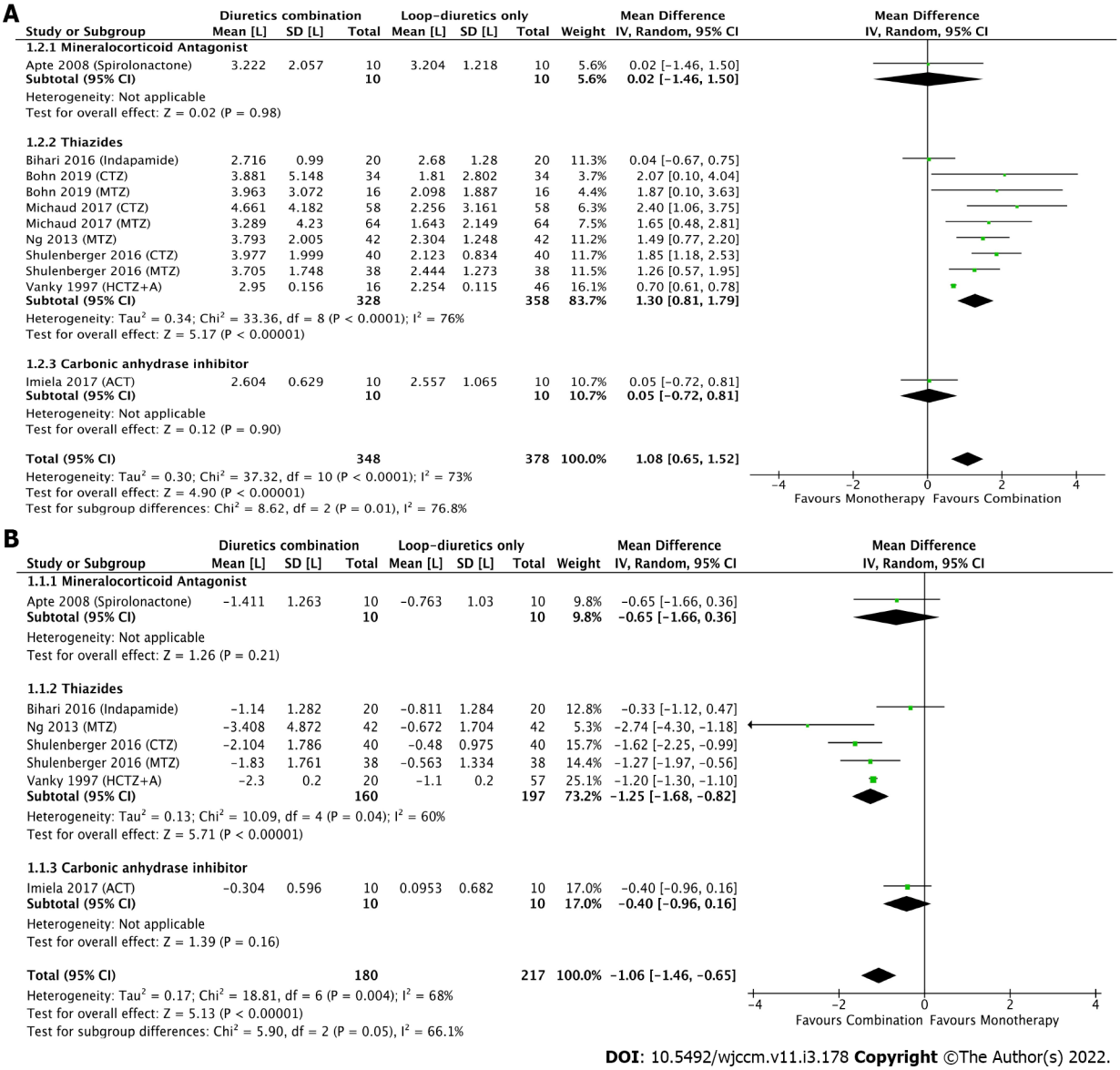

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Figure 2 Forest plot. A: Daily fluid balance; B: Urine output. Comparing loop diuretic in monotherapy to three combinations of diuretics (mineralocorticoid antagonist, thiazides and carbonic anhydrase inhibitor). Mean difference and 95% confidence intervals are shown for each study and the pooled analysis using a random effects model and the Mantel-Haenszel method. Mean difference > 0 means that urine output is higher in the group receiving the combination of diuretics.

literature strategy was limited to generic name. The limited duration of these interventional periods, from 24 to 96 h, may not have substantially affected clinical outcomes such as in-hospital mortality, ICU length-of-stay and ventilation-free survival, which were only partially reported in these studies. Most importantly, the heterogeneity across all included studies was high, including for diuretics doses, renal function, reasons of ICU admission with notable inconsistencies in clinical endpoints reporting. We contacted corresponding authors of all included references to confirm eligibility criteria, but we cannot independently confirm with certainty that all included patients were on mechanical ventilation or required high oxygen volume as some did not respond. Finally, the risk of publication bias is significant, since only limited data has been published in the context of critically ill patients receiving such diuretic strategies.

CONCLUSION

In critically ill patients with respiratory failure receiving a loop diuretic, we showed that addition of another class of diuretic is associated with an increased 24-h urine output leading to a negative fluid balance, where the thiazide and loop-diuretic combination had the higher efficacy. However, given the significant heterogeneity, the risk of publication bias and the lack of adequately powered RCTs, no definitive evidence can be drawn, especially for non-thiazide combinations. In addition, electrolytes

disturbance secondary to the use of these adjunctive diuretics in combination with a loop diuretic warrants additional monitoring to ensure their safety. This limited evidence emphasizes the need for further high-quality trials investigating the efficacy, safety profile and clinical outcomes of such therapeutic interventions for patients with respiratory failure requiring diuretics to control fluid balance.

ARTICLE HIGHLIGHTS

Research background

Diuretics are essential to maintain fluid balance in patients admitted to intensive care units (ICUs). However, resistance to loop-diuretics is common and diuretic combinations are often used in order to mitigate this resistance.

Research motivation

As opposed to patients with heart failure where combinations of different classes of diuretics have been extensively studied and are now recommended, the body of evidence regarding diuretic combinations in ICU patients with hypoxemic respiratory failure is scarce.

Research objectives

This study systematically reviewed the efficacy and safety of common diuretics combinations in ICU patients with respiratory failure when compared to loop-diuretics in monotherapy.

Research methods

A systematic review and meta-analysis were performed. A pooled analysis of the mean difference for the 24-h urine output and the 24-h fluid balance between loop-diuretics in monotherapy and common diuretics combinations (thiazides, carbonic anhydrase inhibitors and mineralocorticoid antagonists) was performed. Descriptive statistics were used to report the occurrence of safety events, such as electrolyte disturbances, hypotension and acute kidney injury.

Research results

From 6510 citations, nine studies totalling 440 patients were included. When compared to loop diuretics alone, the addition of a second diuretic is associated with an improved negative fluid balance at 24 h mean differences (MD) of -1.06 L [95% confidence interval (CI): -1.46; -0.65], mainly driven by the combination of a thiazide plus furosemide [MD: -1.25 L (95%CI: -1.68; -0.82)]. The heterogeneity on the report of clinical and safety endpoints was high, but electrolytes anomalies were frequent and confirms the need for additional monitoring when prescribing such combinations.

Research conclusions

Larger trials are required to confirm the efficacy and safety of diuretic combinations in this population. However, based on limited evidence the combination of thiazide plus loop-diuretics is associated with an increase in urine output and negative fluid balance.

Research perspectives

The study has highlighted the paucity of data on the optimal strategy to optimise fluid balance in patients with respiratory failure and relative diuretics resistance.

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FOOTNOTES

Author contributions: Côté JM, Goulamhoussen N, McMahon BA and Murray PT designed the research study and methodology; Côté JM and Goulamhoussen N performed the research and analyzed the data; Côté JM wrote the draft manuscript; all authors reviewed and approved the final manuscript.

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Country/Territory of origin: Canada

ORCID number: Jean Maxime Côté 0000-0002-3487-2670; Nadir Goulamhoussen 0000-0002-7589-389X; Blaithin A McMahon 0000-0001-8585-2787; Patrick T Murray 0000-0002-0165-6672.

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CASE REPORT

Ball-shaped right atrial mass in renal cell carcinoma: A case report

Sohil Pothiawala, Savan deSilva, Kunzang Norbu

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Sohil Pothiawala, Department of Emergency Medicine, Woodlands Health, Singapore 768024, Singapore

Savan deSilva, Kunzang Norbu, Department of Emergency Medicine, Sengkang General Hospital, Singapore 544886, Singapore

Corresponding author: Sohil Pothiawala, MBBS, MD, Doctor, Department of Emergency Medicine, Woodlands Health, Yishun Central 2, Tower E, Level 5, Yishun Community Hospital, Singapore 768024, Singapore. drsohilpothiawala@yahoo.com

Abstract

BACKGROUND

Renal cell carcinoma (RCC) is an aggressive tumor, with an incidental discovery in most patients. Classic presentation is rare, and it has a high frequency of local and distant metastasis at the time of detection.

CASE SUMMARY

We present a rare case of a 58-year-old man with a ball-shaped thrombus in the right atrium at the time of first incidental identification of RCC in the emergency department. Cardiac metastasis, especially thrombus in the right atrium, is rare. It could either be a bland thrombus or a tumor thrombus, and physicians should consider this potentially fatal complication of RCC early at the time of initial presentation.

CONCLUSION

Ball-shaped lesions in the right atrium are rare, and bland thrombus should be differentiated from tumor thrombus secondary to intracardiac metastasis.

Key Words: Renal cell carcinoma; Metastasis; Tumor thrombus; Bland thrombus; Right atrium; Case report

Core Tip: The classic presentation of renal cell carcinoma is rare, and patients can present with atypical symptoms and local or distant metastasis at the time of initial detection. Cardiac metastasis, especially thrombus in the right atrium, is rare and emergency physicians should consider it early at the time of presentation. Detection of a ball-shaped lesion in the right atrium is rare, and the patient should undergo appropriate evaluation with the aim to differentiate bland thrombus from a tumor thrombus secondary to intracardiac metastasis, as it aids in therapeutic management and prognosis.

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INTRODUCTION

Renal cell carcinoma (RCC) is an aggressive tumor constituting about 3% of all adult malignancies, with a peak incidence in the sixth and seventh decades of life. The classic triad of flank pain, abdominal mass and hematuria is seen in 10% of the cases. Most cases have an incidental discovery[1,2] with local or distant metastases in 25% of the cases at the time of detection. About 10% of these patients have tumor extension into the renal vein and inferior vena cava[3], while only 1% of the total cases have the tumor extending into the right atrium[4]. We present a rare case of a 58-year-old man with a right atrial ball thrombus secondary to metastasis at the time of first incidental identification of RCC in the emergency department (ED).

CASE PRESENTATION

Chief complaints

A 58-year-old man presented to the ED with complaints of breathlessness and reduced effort tolerance for 1 wk.

History of present illness

A 58-year-old man presented to the ED with complaints of breathlessness and reduced effort tolerance for 1 wk. He denied chest pain, orthopnea or paroxysmal nocturnal dyspnea. He also noted a 10 kg weight loss over the last 2 mo. He went to a family physician where he was found to have hematuria and proteinuria on urine examination, and hence referred to the ED. He denied hematuria, lower urinary tract symptoms or fever.

History of past illness

He had no past medical history and was not on any long-term medication.

Physical examination

On presentation, his vital signs were stable but he appeared pale and had bilateral pitting lower limb edema up to the knees. Abdominal examination revealed a left sided large, palpable abdominal mass, but there was no rectal bleeding or melena. Examination of respiratory, cardiac and neurological systems was normal.

Laboratory examinations

His electrocardiogram showed normal sinus rhythm with T-wave inversions and ST-segment flattening in all leads, along with deep T inversions in leads V2-V4. Bedside ultrasound showed a large heterogeneous mass arising from the left kidney suspicious of RCC. Bedside echocardiogram showed a ball-like structure in the right atrium (Figure 1), oscillating between the right atrium and right ventricle intermittently during cardiac cycles, suspicious for a tumor thrombus. There was no pericardial effusion but the right ventricle appeared larger than the left ventricle, suggestive of signs of right heart strain. Blood investigations showed hemoglobin 7.3 g/dL, elevated serum creatinine 155 mol/L (1.75 mg/dL) and N-terminal pro-B type natriuretic peptide 7325 pg/mL. The remaining blood tests, including liver panel, troponin-T, prothrombin time/activated partial thromboplastin time and severe acute respiratory syndrome coronavirus 2 polymerase chain reaction, were normal.

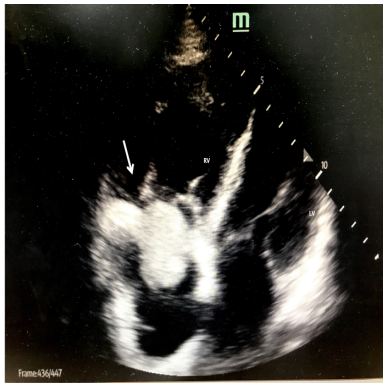

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Figure 1 Bedside ultrasound showing ball-shaped thrombus in the right atrium (arrow).

Imaging examinations

Chest X-ray revealed mild pulmonary venous congestion. Computed tomography (CT) of the abdomen and pelvis (Figure 2) revealed a 13.9 cm × 15.8 cm × 16 cm irregular, heterogeneous left renal mass, suspicious of RCC, with extension of tumor into left renal vein and inferior vena cava (IVC) and metastasis to the liver. CT pulmonary-angiogram showed extensive right pulmonary embolism (Figure 3) with evidence of right heart strain and pulmonary arterial hypertension, as well as pulmonary metastasis (Figure 4). A thrombus was noted in the enlarged right ventricle and right atrial appendage.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient was commenced on subcutaneous enoxaparin 80 mg and admitted to a high dependency unit. Histopathology after imaging-guided biopsy of the left renal tumor revealed clear cell RCC. After discussion at the multidisciplinary tumor board meeting, he was not scheduled for cytoreductive nephrectomy and thrombectomy in view of metastatic burden.

FINAL DIAGNOSIS

He was diagnosed to have left RCC with ball-shaped thrombus in the right atrium, with associated right pulmonary embolism as well as pulmonary metastasis.

TREATMENT

He was treated with enoxaparin 80 mg twice daily and tyrosine kinase inhibitor (TKI) pazopanib 800 mg once daily.

OUTCOME AND FOLLOW-UP

He was discharged and scheduled for outpatient follow-up with a hematologist and oncologist (Figure 5).

DISCUSSION

RCC can present as a solitary metastatic lesion or as a widespread systemic disease, but cardiac metastasis from RCC is extremely rare. The incidence of a thrombus in the right atrium is 0.75%, which is significantly lower than that that of a thrombus in the left atrium[5]. Thrombus in the right atrium is usually located at the atrial appendage or atrial wall. A ball thrombus in the right atrium is even rarer [5].

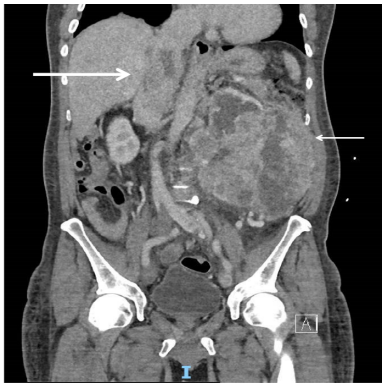

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Figure 2 Computerized tomography scan of abdomen and pelvis showing left renal cell carcinoma (thin arrow) invading in to the hepatic portion of inferior vena cava (thick arrow).

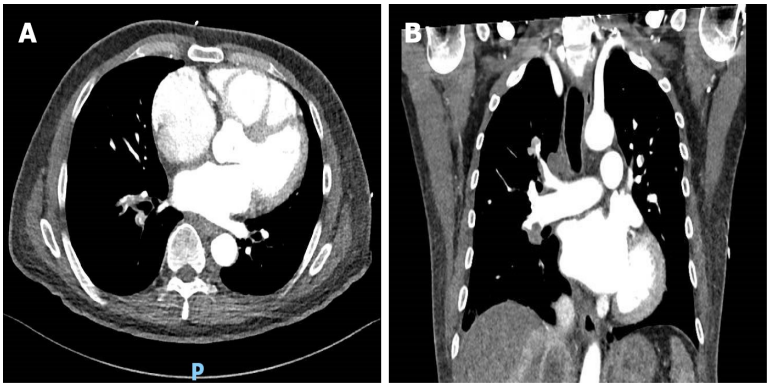

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Figure 3 Large filling-defects in the right segmental and subsegmental branches and right lobar and interlobar arteries suggestive of right-sided pulmonary embolism. A: Right segmental and subsegmental branches; B: Right lobar and interlobar arteries suggestive of right-sided pulmonary embolism.

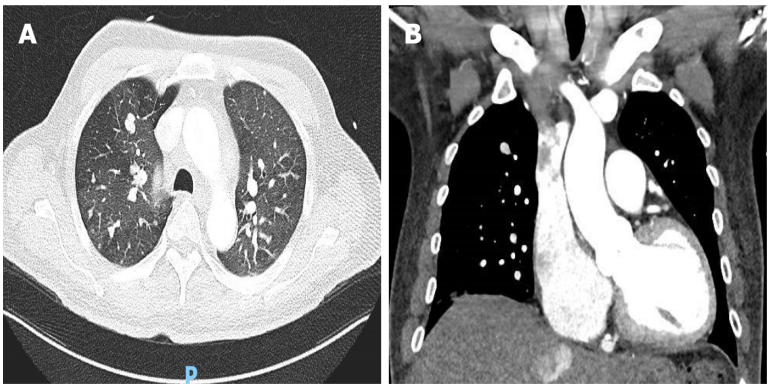

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Figure 4 Multiple pulmonary nodules of varying sizes in the lungs suggestive of pulmonary metastasis. A: Multiple bilateral pulmonary nodules; B: Prominent right sided pulmonary metastasis.

The ball-shaped lesion in our patient's right atrium could either have been a bland thrombus or a tumor thrombus that spread along the IVC. In patients with malignancy, bland thrombus is usually a venous thrombus. Pathogenesis of ball thrombus is still unclear and it can be difficult to make a diagnosis. The challenge is to correctly differentiate bland thrombus from a tumor thrombus secondary to intracardiac metastasis, as it aids in appropriate therapeutic management as well as prognosis. On perfusion magnetic resonance imaging (MRI), heterogeneous enhancement of this ball-shaped lesion

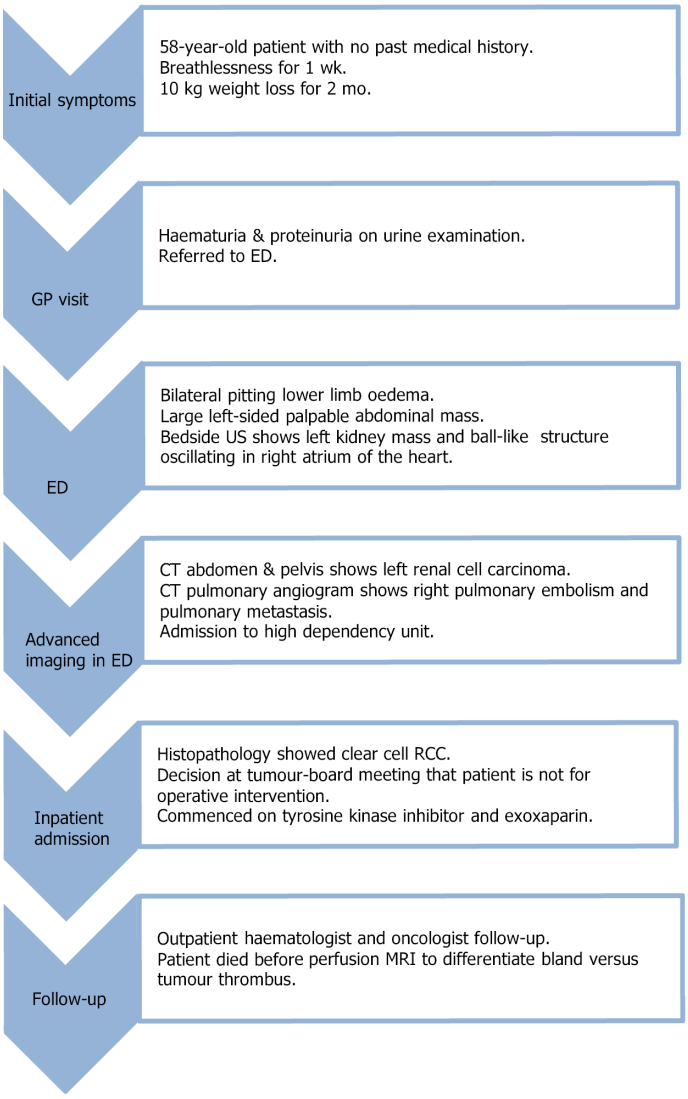

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Figure 5 Timeline following case report guidelines. ED: Emergency department; CT: Computerized tomography; RCC: Renal cell carcinoma; MRI: Magnetic resonance imaging.

and presence of blood products within it suggests a tumor thrombus secondary to RCC metastases. On the contrary, a bland thrombus shows unrestricted diffusion and complete nulling of the mass on MR perfusion imaging[6]. Bland thrombus may resolve after thrombolytic and anticoagulant therapy, unlike tumor thrombus. Our patient unfortunately died before further evaluation could be conducted.

Combining cytoreductive nephrectomy and/or metastasectomy with chemotherapy helps in palliation. The possible surgical option for metastatic RCC extending into the right atrium and causing pulmonary embolism, in this patient, was cardiopulmonary bypass with deep hypothermic circulatory arrest, which is a safe and efficient method for removal of the tumor and thrombus[7]. Manual repositioning of the tumor thrombus out of the right atrium into the IVC on the beating heart is also a safe approach with low risk of tumor thrombembolization[8]. In recent times, the progression free survival has improved due to advances in chemotherapy, immunotherapy and TKI[9]. The overall long-term prognosis of patients with metastatic RCC is poor, with a median survival of 6-12 mo.

CONCLUSION

The classic presentation of RCC is rare, and patients can present with atypical symptoms and local or distant metastasis at the time of initial detection. Cardiac metastasis, especially thrombus in the right atrium, is rare and emergency physicians should consider it early at the time of presentation. Detection of a ball-shaped lesion in the right atrium is rare, and the patient should undergo appropriate evaluation with an aim to differentiate bland thrombus from a tumor thrombus secondary to intracardiac metastasis, as it aids in therapeutic management and prognosis.

FOOTNOTES

Author contributions: Pothiawala S lead conceptualization and wrote the original draft, reviewed and edited the draft; de Silva S and Norbu K wrote the original draft, reviewed and edited the draft.

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ORCID number: Sohil Pothiawala 0000-0002-4789-4326; Savan deSilva 0000-0002-3518-1740; Kunzang Norbu 0000-0002-2475-9578.

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LETTER TO THE EDITOR

Ideal scoring system for acute pancreatitis: Quest for the Holy Grail

Deven Juneja

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Deven Juneja, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi 110017, India

Corresponding author: Deven Juneja, DNB, FCCP, MBBS, Director, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, 1, Press Enclave Road, Saket, New Delhi 110017, India. devenjuneja@gmail.com

Abstract

Clinical scoring systems are required to predict complications, severity, need for intensive care unit admission, and mortality in patients with acute pancreatitis. Over the years, many scores have been developed, tested, and compared for their efficacy and accuracy. An ideal score should be rapid, reliable, and validated in different patient populations and geographical areas and should not lose relevance over time. A combination of scores or serial monitoring of a single score may increase their efficacy.

Key Words: Acute pancreatitis; Scoring systems; Sequential organ failure assessment score

Core Tip: A score which is rapid, reproducible, reliable, and validated across different patient populations is ideally required to predict outcomes in acute pancreatitis. As most of the scores have similar efficacy, the choice of score in a particular center may depend on ease of computation and application. Sequential organ failure assessment score has been validated in various patient populations, is easy to compute and apply, and has withstood the test of time. Hence, it may be a good option, to predict outcomes in patients with acute pancreatitis.

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TO THE EDITOR

We read with interest the retrospective analysis of 653 patients with acute pancreatitis

(AP) by Teng *et al*[1], in which they compared the efficacy of six clinical scores to predict outcomes. The authors concluded that even though both sequential organ failure assessment (SOFA) and 48-h Ranson's score could accurately predict the severity, need for intensive care unit (ICU) admission, and mortality in patients with AP, SOFA score had more favourable statistics.

Scoring systems are commonly employed to assess the need for ICU, to compare groups of patients, and to predict complications and outcomes. Many a time, these scoring systems are developed and tested in particular patient populations like patients with sepsis, AP, and chronic liver disease. Some scoring systems can be applied to general ICU patients. Many scores can be computed at the time of admission but certain others have to be calculated 24-48 h after admission. With improvements in healthcare standards and availability of modern healthcare equipment, patient outcomes may also improve over time, making older scores lose relevance. Hence, these scores need to be tested and compared for their efficacy and accuracy in different patient populations, different geographical areas and over different time periods.

Severe AP is associated with high morbidity and mortality and hence, early recognition of patients at risk of developing complications and poor outcomes is required to institute early aggressive care, and improve outcomes. Many scores have been specifically developed for predicting outcomes of patients with AP, and these include Ranson's, Glasgow, Pancreatitis outcome prediction (POP), bedside index of severity in acute pancreatitis, and Harmless AP scores. These have been compared with each other and also with other scores designed for general ICU patients like Acute Physiology and Chronic Health Assessment (APACHE), simplified acute physiology score (SAPS), and SOFA scores. However, no single score has been found to be an ideal score, able to accurately identify the patients at risk and predict outcomes in different clinical conditions. Hence, newer scores are being developed and tested against the existing scores[2]. But before these scores are routinely used, they need to be meticulously tested in varied patient populations, over a period of time.

In a similar prospective cohort study conducted in ICU patients, we compared ten scores: APACHE II and III, SAPS II, mortality probability models II, SOFA score, Logistic Organ Dysfunction System, Multiple Organ Dysfunction Score, Ranson, modified Glasgow, and POP[3]. As with the analysis of Teng *et al*[1], we also could not identify a single ideal score but SOFA score had the best statistics in predicting severity and mortality in patients with AP. SOFA score > 8 had a sensitivity and specificity of 87% and 90%, respectively, in predicting 30-d mortality[3]. Our study is more than a decade old but SOFA score still seems to be efficacious in predicting outcomes of patients with AP.

SOFA score was originally developed to describe organ failure in patients with sepsis and was termed "Sepsis-related Organ Failure Assessment"[4]. Subsequently its utility in other patient populations have been tested and validated. It has been compared to other severity of illness scores and has shown good accuracy to predict outcomes in varied patient populations. Expanding the role of SOFA score, different modifications have been suggested to improve its accuracy in specific patient populations like pSOFA for paediatric patients, CLIF-SOFA for chronic liver disease, SOFA-HM for haematological malignancies, and qSOFA and lactic acid SOFA for patients in emergency rooms[5]. Even the latest sepsis definitions recommend using SOFA score for diagnosis of sepsis and septic shock [6].

Now, in the age of artificial intelligence (AI), machine learning algorithms have been developed to predict severity, complications, recurrence, mortality, and even timing for surgery in patients with AP, with good accuracy[7]. However, the quality of the studies assessing the accuracy of AI remains low and there is a dearth of studies comparing AI with these commonly applied clinical scores. Hence, more studies need to be done before we routinely start using AI in our daily routine clinical practice. Till then, SOFA score, which is easy to compute and apply, seems to be the most reasonable choice.

FOOTNOTES

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Country/Territory of origin: India

ORCID number: Deven Juneja 0000-0002-8841-5678.

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