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ABOUT COVER

Peer Reviewer of *World Journal of Critical Care Medicine*, Deven Juneja, DNB, FCCP, MBBS, Doctor, Department of Critical Care Medicine, Max Super Speciality Hospital, New Delhi 110017, India. devenjuneja@gmail.com

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MINIREVIEWS

Point-of-care ultrasound for critically-ill patients: A mini-review of key diagnostic features and protocols

Yie Hui Lau, Kay Choong See

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Yie Hui Lau, Department of Anaesthesiology, Intensive Care and Pain Medicine, Tan Tock Seng Hospital, Singapore 308433, Singapore

Kay Choong See, Division of Respiratory & Critical Care Medicine, National University Hospital, Singapore 119074, Singapore

Corresponding author: Yie Hui Lau, MBBS, Doctor, Department of Anaesthesiology, Intensive Care and Pain Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore. yie_hui_lau@ttsh.com.sg

Abstract

Point-of-care ultrasonography (POCUS) for managing critically ill patients is increasingly performed by intensivists or emergency physicians. Results of needs surveys among intensivists reveal emphasis on basic cardiac, lung and abdominal ultrasound, which are the commonest POCUS modalities in the intensive care unit. We therefore aim to describe the key diagnostic features of basic cardiac, lung and abdominal ultrasound as practised by intensivists or emergency physicians in terms of accuracy (sensitivity, specificity), clinical utility and limitations. We also aim to explore POCUS protocols that integrate basic cardiac, lung and abdominal ultrasound, and highlight areas for future research.

Key Words: Critical care; Echocardiography; Point-of-care testing; Sensitivity and specificity; Ultrasonography

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Core Tip: Point-of-care ultrasound (POCUS) is increasingly being used by intensivists and emergency physicians for the care of critically-ill patients. This mini-review highlights key findings in basic cardiac, lung and abdominal ultrasound, and introduces several POCUS-based protocols, which have practical utility for patient management.

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INTRODUCTION

Diagnostic errors in medicine and intensive care are prevalent, with autopsy studies showing substantial misdiagnoses[1]. Point-of-care ultrasonography (POCUS) fills a void to reduce diagnostic uncertainty and some features may also guide prognosis and management. However, image acquisition and interpretation needs to be done with skill and caution to avoid inadvertent over- or underdiagnosis of abnormalities. POCUS misdiagnoses due to inexperience may lead to errors in the treatment that may worsen patients' outcomes or even be fatal[2]. Each POCUS practitioner must be mindful of this, and follow up or evaluate with alternatives where applicable. It is still important that any form of POCUS should be preceded by clinical examination, which provides complementary information for diagnosis and treatment.

There is an increase in the application of POCUS for managing critically ill patients, performed by intensivists or emergency physicians, who are neither radiologists nor sonographers. POCUS is inexpensive, non-invasive and can be readily available at the bedside. It is thus an important skill-set for anyone who takes care of critically ill patients.

POCUS may be too brief to have in depth interrogation of any pathology found and more detailed scanning is not practical in a busy intensive care unit (ICU) or emergency department. Excessive time taken for image acquisition and measurements may delay other clinical assessment or treatment. If abnormalities are found or if a comprehensive evaluation is required, a formal transthoracic echocardiogram or follow up computed tomography (CT) imaging can then be arranged at a more opportune time.

Results of needs surveys among intensivists reveal emphasis on basic cardiac, lung and abdominal ultrasound[3], which are the commonest POCUS modalities in the ICU. We thus aim to describe the key diagnostic features of basic cardiac, lung and abdominal ultrasound as practised by intensivists or emergency physicians in terms of accuracy (sensitivity, specificity), clinical utility and limitations. We also aim to explore POCUS-based protocols that integrate these ultrasound features.

BASIC CRITICAL CARE ECHOCARDIOGRAPHY

Basic critical care echocardiography (CCE) typically involves obtaining 4 echocardiography views (parasternal long axis, parasternal short axis, apical four- chamber, subcostal views) to answer urgent questions at the bedside, regarding myocardial contractility, left ventricular filling, right ventricular dilatation, or the presence of other obvious abnormalities (*e.g.* large pericardial effusion). Myocardial contractility is usually described in terms of regional wall motion abnormalities such as hypokinesia, dyskinesia or akinesia. Image acquisition and interpretation requiring all 4 of these views require skill and competency in order to complete the assessment in a timely manner. CCE is most often used to evaluate causes of shock, cardiac arrest or acute cardiopulmonary failure. Some key features of basic CCE are summarised in Table 1; examples in Figure 1.

BASIC LUNG ULTRASOUND

Lung ultrasound has also gained popularity because of its relative portability. The added benefit compared to chest radiographs and CT imaging, is that the patient's clinical course can be conveniently followed up over time with no radiation risk. Lung ultrasound has been shown to reduce the use of chest radiographs and CT scans in critically ill patients by 26% and 47% respectively[4]. The diagnostic accuracy rates of lung ultrasound for cardiogenic pulmonary edema (94% *vs* 65%, $P = 0.03$) and for pneumonia (83% *vs* 66% $P = 0.016$) are better if paired with CCE, than compared to lung ultrasound alone[5]. Some of the key features and the clinical utility of these features are described in Table 2, with examples in Figure 2.

General limitations to lung ultrasound include a large body habitus, presence of subcutaneous emphysema and thoracic dressings; these limit obtaining adequate windows[6]. Lack of access to training and ultrasound machines also limit more widespread application of lung ultrasound. However, compared to CCE, competency in lung ultrasound can be achieved more quickly with a minimum of 10 scans[7].

ABDOMINAL ULTRASOUND

While basic cardiac and lung ultrasound features have generally been well-characterized individually, abdominal ultrasound features have instead been studied in the context of integrated protocols. The Focused Assessment with Sonography for Trauma (FAST) incorporates scanning the abdomen, heart, pericardial and pleural spaces in a trauma patient. This subsequently incorporated basic thoracic injury

Table 1 Characteristics of basic critical care echocardiography

	Key features	Accuracy % (95%CI)	Clinical utility	Limitations
Pericardial effusion	Echo-free space between heart and the parietal layer of the pericardium. 15 mL: Minimum detectable by echocardiography; > 50 mL: Pathological. Nature of the fluid-non-echogenic space (serous fluid), echogenic fluid (blood, pus)	ED physicians using a combination of parasternal short and long axis, apical and subcostal views: (1) Sensitivity 96 (90.4-98.9); (2) Specificity 98 (95.7-98.7); (3) PPV 92.5 (85.8- 96.7); and (4) NPV 98.9 (97.3-99.7). Accuracy: 97.5 (95.7-98.7)[29]	Diagnostic, as a cause of dyspnea; Characterisation of fluid; Estimate size of effusion; Guide approach for pericardiocentesis	Pleural effusion, pericardial fat pad may be mistaken as pericardial effusion. Limited echo windows may affect the sensitivity and specificity of CCE. 4 standard views should be done to assess if the effusion is localised or global[30]
Pericardial tamponade	A pericardial effusion with: (1) Diastolic RV collapse; (2) Systolic RA collapse < 1/3 of cardiac cycle (earliest sign); (3) A plethoric IVC with minimal respiratory variation; and (4) Doppler: Exaggerated respiratory cycle changes in mitral and tricuspid valve in-flow velocities (peak E wave velocity will drop at least 25% (mitral) 40% (tricuspid) in expiration compared to inspiration (suggestive of pulsus paradoxus)	(1) Sensitivity 48-60; Specificity 75-90[31] (sensitivity and specificity improves as the severity increases); (2) RA collapse. Sensitivity 55-97; Specificity 33-100[31]. Absence of both RA systolic, RV diastolic collapse: NPPV 90; Sensitivity 95-97; Specificity 40; (3) Sensitivity 92% but not specific[32]; and (4) Pulsus paradoxus itself: Sensitivity 82% (95%CI: 72%–92%); in the presence of pericardial effusion, positive LR 3.3 (95%CI: 1.8-6.3) and negative LR 0.03 (95%CI: 0.01-0.24)[31]	Identifying tamponade as cause of shock. If found to be the cause of cardiac arrest, and had pericardiocentesis after diagnosis, survival to discharge increased by 15.4% (compared to 1.4% without POCUS)[33]	(1) Plethoric IVC may be caused by chronic lung disease, congestive cardiac failure, tricuspid regurgitation; (2) Patients on mechanical ventilation will not demonstrate plethora because inspiration is generated by positive pressure and hence IVC expands rather than collapses[34]; (3) Doppler techniques require more advanced practitioners of POCUS; and (4) Respiratory variation of the mitral and tricuspid inflows should not be used as a sole criterion for tamponade without the presence of chamber collapse, IVC dilation, or abnormal hepatic vein flows (blunting or reversal of diastolic flows in expiration)
Right ventricular dilation and dysfunction	(1) RV dilatation in PE: Diameter-> 42 mm (base), > 35 mm (mid-level). Longitudinal dimension > 86 mm[35]; (2) RV dysfunction in PE, TAPSE < 17.5 mm, indicated abnormal, RV systolic, function[36]; (3) RV hypokinesis; (4) Right heart thrombi; (5) Ventricular interdependence; (6) Leftward septal displacement; and (7) McConnell sign (Normal contraction or sparing of the RV apex with hypokinesis of midportion of the RV free wall)	(1) Enlargement of the RV compared to the LV. Sensitivity 55. Specificity 86[37]; (2) RV dysfunction indicated by abnormal TAPSE Sensitivity 87. Specificity 91. AUC 0.96 (95%CI: 0.87-1.00)[36]; (3) RV hypokinesis for diagnosis of PE. Sensitivity 70. Specificity 33. Predictor of 30-d mortality in PE. Sensitivity 52.4 (43.7-61.0). Specificity 62.7 (59.5-65.8). NPV 90.6 (88.1-92.7). PPV 16.1 (12.8-19.9)[38]; (4) –; (5) –; (6) –; and (7) Sensitivity 70%. Specificity 33; PPV 67; NNV 36 [30]	To identify acute cor pulmonale or pulmonary embolism. Various echocardiographic signs can be used to rule in PE, but none can rule it out. This is due to the known variability of PE presentation, clot burden, and physiologic reserve that contribute to pulmonary vascular resistance and acute RH strain[36]. RV dysfunction in PE found to be predictor of early mortality[38]. Presence of right heart thrombi is associated with an increased risk of death in 30 d	Obtaining adequate RV views in critically ill patients may be challenging, especially post abdominal-surgery with a smaller subcostal window. There are numerous methods available to measure RV size and function, yet the parameter that is the most accurate in the critically ill is controversial[39]. McConnell's sign may also be present in RV infarct and not just PE (*i.e.* Not specific for PE)
Left ventricular dysfunction [40]	(1) 2D Biplane; (2) Visual ejection fraction; (3) MAPSE < 12 mm; and (4) E-point septal separation > 7 mm	(1) -; (2) Predicts LVEF < 50%. AUROC 0.8 (0.70-0.90); (3) Predicts LVEF < 50% AUROC 0.73 (0.62-0.84); and (4) Predicts EF < 30%. Sensitivity 100 (95%CI: 62.9-100). Specificity 51.6 (95% CI: 38.6-64.5)[41]	(1) Allows more informed risk counselling, prognostication. Patients with no cardiac activity on PoCUS were much less likely to achieve ROSC, had shorter mean resuscitation times[42]; and (2) Relatively easy and rapid. Internal Medicine physicians were able to identify normal versus decreased LVSF with high sensitivity, specificity, and "good" interrater agreement compared to formal echocardiography after completing a training program[43]	(1) Requires optimal acquisition of endocardial borders, time consuming, requires training; (2) and (3) are rarely done
Variation of IVC diameter with respiration	(1) Collapsibility index, measured 4cm caudal to the right atrium, with a deep standardised inspiration; (2) Distensibility index during intermittent positive pressure ventilation; and (3) IVC collapse of > 50 %	(1) Fluid responsiveness: Depending on whether a standardised or non- standardised spontaneous breath was taken: Sensitivity 66-93 Specificity 99-98[44,45]; (2) Comparable to pulse pressure variation in predicting fluid responsiveness (AUROC 0.75 ± 0.07); (3) Cut off value of 16.5%. Sensitivity 71.4; Specificity 76.5[46]; and (4) In predicting CVP < 8 mmHg: PPV of 87, NPV of 96,	Assessment of fluid responsiveness to avoid unnecessarily fluid boluses. The degree to which the CVP falls during spontaneous inspiration depends upon 3 variables: Cardiac function; The drop in pleural pressure; Venous return	Requires a spontaneously breathing patient, able to cooperate and perform a standardised breath. Accuracy affected by point of measurement along the IVC and the angle of insonation, given the cylindrical nature of the IVC and especially for the use of M-Mode measurements. IVC may be dilated in valvulopathies, pulmonary hypertension or in highly trained athletes[25]. May not accurately indicate volume status because venous return can be affected by

	AUROC 0.93	other factors *e.g.* vascular tone. IVC collapsibility may be confounded by pressure within the abdominal cavity *e.g.* Intra-abdominal hypertension, ascites, IPPV

AUROC: Area under receiver operating characteristic; CVP: Central venous pressure; ED: Emergency department; IPPV: Intermittent positive pressure ventilation; IVC: Inferior vena cava (plethoric IVC defined as diameter > 2.1 cm and < 50% inspiratory reduction); LR: Likelihood ratio; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVSF: Left ventricular systolic function; MAPSE: Mitral annular plane systolic excursion; NPV: Negative predictive value; PE: Pulmonary embolism; PPV: Positive predictive value; RA: Right atrial; ROSC: Return of spontaneous circulation; RV: Right ventricle; TAPSE: Tricuspid annular plane systolic excursion.

assessment in form of extended FAST (E-FAST). In FAST, abdominal sonography focuses on detecting free fluid in the abdominal cavity which indicates hemoperitoneum associated with significant abdominal injuries. The 4 sonographic views in the FAST exam are the 4 Ps: Pericardial, perihepatic, perisplenic, pelvic regions. The limitations of FAST are that it has low accuracy in the very early post-injury phase, and does not detect retroperitoneal bleeding well. It does not detect early solid organ injuries not accompanied by significant bleeding. It does not replace traditional imaging modalities if there are penetrating injuries[8]. Extended FAST further incorporates basic lung ultrasound to detect pneumothoraces or hemothorax, which has a sensitivity of 78.6%-95.3% (68.1%-99.2%) and specificity of 98.2%-99.8% (97.0%-99.9%) compared to traditional clinical examination and radiological imaging with chest X-ray or CT[8]. Other than FAST, abdominal POCUS in the critical care setting also includes assessing the bladder (to detect retention of urine), kidneys (for hydronephrosis *etc.*), gallbladder (for cholecystitis *etc.*), and abdominal aorta (for abdominal aortic aneurysms). Some examples are shown in Figure 3.

POCUS PROTOCOLS

Since 2001, intensivists and emergency physicians have come up with protocols that integrate the key features of basic cardiac, lung and abdominal ultrasound. These protocols are used to confirm or eliminate certain diagnoses in a stepwise manner. Clinicians perform POCUS as an extension of the physical examination in a problem-oriented approach, and scans are often repeated post intervention.

As with all ultrasound procedures, POCUS is operator dependent. Some of the protocols described also require advanced CCE competencies. The more recent protocols tend to integrate multiple POCUS modalities, and have stepwise diagnostic questions to be answered depending on the clinical context. For lung ultrasound, different protocols have different number of points to assess, which is based on the clinical experience of the authors. Some other examples, which are used to explore causes of shock and cardiac arrest, are listed in Table 3. We also included some protocols which only involved one POCUS modality due to its integration in other protocols (BLUE protocol)[9], or the unique pathophysiological question it tries to answer (VeXUS)[10]. The clinical benefits of the protocols described below are still pending further study.

The C.A.U.S.E. protocol[11] aims to detect the common diagnoses that may explain a cardiac arrest, such as cardiac tamponade, severe hypovolemia, pulmonary embolism and pneumothorax. It involves 2 sonographic perspectives of the thorax: The 4 chamber view (the subcostal view is recommended), and the anteromedial views of the lung and pleura at the second intercostal space, at the midclavicular line.

Table 2 Characteristics of basic lung ultrasound

	Key features	Accuracy %	Clinical utility	Limitations
A-Pattern	Horizontal artifact indicating normal lung surface indicating PAOP ≤ 13 mmHg	Sensitivity 67; Specificity 90 [47]	Dry inter-lobular septa. Aeration, response to PEEP and recruitment. Diagnosis/exclusion of large PE	For diagnosis of PE, requires ability to perform DVT scans to support findings. A-pattern may manifest in large pulmonary embolism but not in cases of smaller pulmonary emboli in the peripheral lung parenchyma near the pleural surface may be detected by lung ultrasound[48], classical described as hypoechoic, pleural-based parenchymal alteration with > 85% of these lesions wedge-shaped[49]. A-lines may be seen in cases of pneumothorax, COPD/asthma
Pneumothorax	May have A pattern due to reflection of air at the parietal pleura. During M-Mode: (1) "Stratosphere"/"Bar code" sign, instead of a seashore sign. During B-Mode; (2) Loss of lung sliding; and (3) Lung point-transition of normal lung sliding/B lines to a pneumothorax pattern (no lung sliding or B lines) at a critical point, during a respiratory cycle	(1) Sensitivity 86-91, Specificity 91-99[6,50]; (2) Sensitivity 67, Specificity 100, PPV 100, NPV 91; and (3) Sensitivity 66. Specificity 100[51]	Early detection in trauma in the emergency department, even for non-radiologists	Absence of "lung sliding" alone may not confirm the presence of pneumothorax. Small, apical pneumothoraces may be false negatives but usually do not require any intervention. False positives in non-trauma critically ill patients due to: (1) Dyspnea; (2) Single lung intubation or esophageal intubation; (3) Lung and pleura adhering together due to ARDS/chronic pleurodesis, cancer, phrenic nerve palsy, large infiltrates/pleural effusion, pulmonary contusions; and (4) Presence of several A lines in patients with asthma/COPD[52]
Occult pneumothorax (detected on CT scan but missed on chest radiography)	(1) Abolition of lung sliding alone; (2) Absent lung sliding plus the A line sign. The A line sign is the presence of A-lines *without* associated B lines (In normal lung, A lines will be with artifacts such as B lines, and lung sliding); also known as the stratosphere sign; and (3) The lung point	(1) Sensitivity 100, Specificity 78; (2) Sensitivity 95, Specificity 94; and (3) Sensitivity 79, Specificity 100[53]	Reduced need for CT scans, transportation, ionising radiation. Earlier detection of pneumothorax.	Among controls without pneumothorax, some may have absent lung sliding (false positive)
B-profile	B-lines are vertical ring-down artifacts that do not fade with increasing depth, and move with lung sliding, and obliterate A lines. > 3 is considered pathological. Alveolar-interstitial syndrome. > 2 Comet-tails 7 mm apart, indicating thickened interlobular septa	Sensitivity 97-98, Specificity88-95[54]	Diagnosis of acute hemodynamic pulmonary edema. Other differentials: Generalised–acute or chronic interstitial lung disease, acute lung injury/acute respiratory distress syndrome. Focal–related to pneumonia, pulmonary contusion, lung tumours, other pulmonary consolidating processes[55]. May be due to Gravity-related dependent edema may be present in dependent areas. May be used with other POCUS modalities *e.g.* CCE to diagnose underlying cause of interstitial syndrome	Comet tails, which are short (1cm) reverberation artifacts, may be mistaken as B-lines. Unlike B-lines, comet tails do not obliterate A-lines, fades with increasing depth. They may be present in normal lung[55]. Lacks utility in patient with known pre-existing interstitial syndrome unless there

				are prior scans for comparison. False positives: (1) Physiological B-lines may be present in 10% of healthy population; and (2) Older persons may have more B-lines and chest areas positive
Consolidation	Hypoechoic tissue with hyperechoic punctiform images (air-bronchograms). C-profile in the BLUE protocol: Anterior lung consolidation or thick, irregular pleural line[40]	Sensitivity 92-93, Specificity 92-100[54,56]		Atelectasis may appear similar and be misinterpreted as consolidation (false positive). This can be differentiated from consolidation by the lung pulse and dynamic air bronchogram[57]
Pleural effusion	Fluid collection in pleural space, above diaphragm. Able to detect as little as 15 mm. Quantification of amount of pleural effusion: A pleural effusion ≥ 800 mL is predicted when interpleural distance was > 45 mm (right) or > 50 mm (left)	Sensitivity 91-93, Specificity 92-93[56] (Right side) Sensitivity 94, Specificity 76 (Left side), Sensitivity 100, Specificity 67	Non-invasive, radiation-free detection of pleural effusion which can also guide bedside drainage. Avoids need for transportation for CT-imaging. May show features which further characterises the type of effusion; septations, debris, heterogeneous fluid collections which are suggestive of an exudative effusion; anechoic, homogenous fluid which suggests transudative effusion. Guides location for thoracocentesis. At least 2 cm of interpleural distance required as a minimum indication for thoracocentesis	In patients with an elevated hemidiaphragm, inappropriate diaphragm visualization may lead to mistaking effusion for sub-diaphragmatic ascites. May be confused with pericardial effusion. Peri-procedure complications and injury may occur if the heart/subdiaphragmatic organs are overlooked thinking a pericardial/subdiaphragmatic effusion is a pleural effusion. Loculated effusions may be missed or misjudged with inadequate scanning especially in posterior areas

ARDS: Acute respiratory distress syndrome; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; DVT: Deep vein thrombosis PAOP: Pulmonary artery occlusion pressure; PE: Pulmonary embolism; PEEP: Positive end expiratory pressure; PLAPS: Posterolateral alveolar and/or pleural syndrome, a posterior continuation of the lower BLUE point.

The SESAME protocol[12] was initially described for shock or cardiac arrest, aiming to identify the commonest causes, or easiest causes to diagnose or manage. It uses a single microconvex probe which is available on most ultrasound systems. The steps are as follows: (1) Lung ultrasound (BLUE followed by FALLS protocol), because of convenience and it quickly indicates if a fluid challenge is appropriate; (2) Lower femoral vein vascular ultrasound or abdominal ultrasound to detect deep vein thrombosis or free fluid in the abdomen respectively; and (3) This is followed by pericardial and cardiac ultrasound. The benefit of this protocol is that it uses a single "universal" probe which saves time in a crisis.

The PIEPEAR[13] protocol is a 7-step protocol used in the setting of acute clinical deterioration of a critically ill patient. It describes a thought process, and incorporates POCUS assessments: (1) Identifying deranged physiological systems; (2) Screening for causes; (3) Focused ultrasound exam; (4) Making a presumptive diagnosis; (5) Exploring an etiology, including other investigations; (6) Initiating treatment; and (7) Repeating the focused ultrasound to assess the response to treatment, and titrating the treatment accordingly. It includes a 12-step lung and cardiac ultrasound sequence involving inferior vena cava (IVC), right ventricle (RV), left ventricle (LV) systolic and diastolic function, and afterload

Table 3 Point-of-care ultrasonography protocols in intensive care unit and emergency departments

Modalities used	Protocols (Year described)	Clinical utility	Limitations
Lung ultrasound only	BLUE protocol[9] (2008). (1) Nude profile (No abnormalities, A-profile with no DVT); (2) B-profile: Anterior lung rockets with lung sliding. Causes: Acute pulmonary oedema; (3) Pulmonary embolism (A-profile with DVT); (4) Pneumothorax (A'-profile with lung point); and (5) Pneumonia, 4 profiles (B' profile, A/B, C-profile, no-V-PLAPS profile)	Diagnosis in acute respiratory failure. A simple, dichotomous protocol which uses a single microconvex probe without need for advanced techniques (1) Accuracy 90.5%, Sensitivity 89%, Specificity 97%, PPV 87%, NPV 99%; (2) Sensitivity 97% (89%-100%), Specificity 95% (91%-98%)[9, 58], LR+ 21.1, LR- 0.03; (3) Sensitivity 81% (58%-95%), Specificity 99% (98%-100%), LR+ 193, LR- 0.19; (4) Sensitivity 88% (52%-100%) Specificity 100% (99%-100%), LR+ (infinity), LR- 0.11; and (5) All 4 profiles: Sensitivity 89 (80%-95%), Specificity: 94 (90%-97%), LR+ (15.8), LR- (0.11)	Pneumonia can generate a B-profile without anterior consolidation. Initial publication excluded patients post hoc with multiple diagnoses
Abdominal ultrasound only	VExUS[10] (2020). Evaluates IVC congestion and severity of congestion in 3 organs: Liver, gut, kidneys	(1) Indicates risk of post-cardiac surgery acute kidney injury related to venous congestion; (2) Potentially may guide fluid interventions to improve organ perfusion; and (3) Severe VExUS grade C and subsequent development of subsequent AKI after cardiac surgery. Sensitivity 27% (CI 15%-47%); Specificity 96% (CI 89%-99%) (+LR: 6.37 CI 2.19-18.5)	(1) Does not identify the source of venous congestion; (2) Currently not yet validated in other clinical settings or successful interventions to change outcomes; (3) Includes difficult and complex image acquisition and measurements; (4) Hepatic vein Doppler may be influenced by tricuspid regurgitation; pulsatile portal vein flow and IVC dilatation have been reported in healthy athletic volunteers (potential false positive)[10]; and (5) Hepatic and portal vein Doppler waveforms may be abnormal in cirrhotics due to arterio-portal shunting, such as reversal of portal venous flow; pulsatile or helical portal venous flow[59]
Cardiac and lung ultrasound	C.A.U.S.E[11] (2008). 4 chamber view of the heart + lung ultrasound. Diagnosis of (1) Pericardial tamponade; (2) Tension pneumothorax; (3) Pulmonary embolus; and (4) Hypovolemia	Aims to detect the 4 leading causes of non-arrhythmogenic cardiac arrest without interfering with resuscitation (1) Poor to moderate sensitivity as routine screening in all patients suspected of pulmonary emboli, but good to excellent specificity; and (2) Collapsed IVC or < 5 mm should prompt fluid resuscitation. > 20 mm suggests pump failure (congestive heart failure, cardiac tamponade, PE)	
	FALLS (Fluid Administration Limited by Lung Sonography) protocol[60] 2013. Combines CCE and BLUE-protocol lung ultrasound to assess causes of circulatory failure	(1) For expediting a diagnosis; (2) Guides fluid management in acute circulatory failure *e.g.* cessation of inappropriate fluid boluses; (3) Sequentially rules out obstructive, cardiogenic, then hypovolemic shock for expediting the diagnosis of distributive (usually septic) shock[60]; and (4) Allows earlier fluid therapy before confirmation of sepsis	(1) Absence of cardiac windows will limit earlier parts of the protocol, requires lung ultrasound (PE section); (2) Presence of diffuse lung rockets (B-profile, B' profile) on initial assessment will exclude patients from this protocol because fluid administration cannot be guided by transformation of A-lines to B-lines, but fluids can be given using other POCUS findings; and (3) Cardiogenic shock due to RV failure (with low wedge pressure) will not be easily diagnosed as it is usually associated with A-profile. Do ECG to rule out right sided myocardial infarction
	ORACLE[15] (2020). O: Left ventricular functiOn, R = Right ventricular disease, A = vAlve disease, C = periCardium, L = Lung ultrasound, E = hEmodynamic parameters	(1) ICU, COVID-19 patients; and (2) Cardiac and pulmonary evaluations	(1) Intermediate to advanced echo skills required with several measurements required; and (2) Requires at least 20 min in trained hands, may take longer for novices
	PIEPIER (2018)[13]. 12 step lung ultrasound + CCE: IVC, RV, LV systolic and diastolic function, and afterload deduction/calculation	A stepwise approach to diagnosing causes of cardio-respiratory failure, including consideration of etiology, interventions and reassessments	Requires experience for image interpretation, diagnosis and intermediate echocardiography
Cardiac, lung, venous	ASE POCUS protocol for COVID-19 pandemic[16] (2020). (1) Cardiac (basic views); (2) Lung (8 or 12 point); and (3) Vascular [IVC, leg veins (optional)]	(1) Outlines structures to be imaged, parameters to assess and measure, and disease associations; (2) May assist in the initial cardiopulmonary assessment of patients with COVID-19; (3) Also includes device cleaning checklist; and (4) Mentions need for storing and documenting POCUS results to reduce the need for repeat examination	In the case of difficult image acquisition, and it may be more efficient for a skilled sonographer to rapidly scan the patient, rather than have a POCUS operator struggle with prolonged attempts

Cardiac, lung and abdominal ultrasound	SHoC-ED[42] (2018). Combines ACES (abdominal and cardiothoracic evaluation with sonography in shock), and RUSH (rapid ultrasound in Shock and Hypotension)	Cardiac: Assess LV/RV function, size and presence of pericardial effusion. Lung: Base of lung-lung sliding. Abdominal-free fluid, AAA, IVC for size and collapsibility	An RCT in ED involving patients with undifferentiated hypotension did not detect significant difference in 30 d or hospital survival, media fluid administered, inotrope administration
Cardiac, lung, venous and abdominal	GUCCI (2019)[14]. (1) Acute respiratory failure: Lung ultrasound + cardiac + vascular ultrasound; and (2) Shock: Cardiac + lung + vascular + abdominal ultrasound	Guide diagnosis and interventions in acute respiratory failure, shock and cardiac arrest (*e.g.* Defibrillation)	Needs competency in other modes of POCUS
	SESAME (2015)[12]. 5 steps: (1) Lung ultrasound (BLUE followed by FALLS protocol); (2) Lower femoral vein vascular ultrasound "V-point": A distal, lower superficial femoral vein; (3) Abdominal ultrasound; (4) Pericardium; and (5) Cardiac ultrasound	Severe shock or cardiac arrest. Assess for tension pneumothorax, hypovolemia, pulmonary embolism, pericardial tamponade, free abdominal fluid as a cause of cardiac arrest	(1) Uses a single microconvex probe, which may not be available on all ultrasound systems; (2) Limitations due to body habitus; (3) Evaluates for VTE only at the "V-point", which is different from other VTE POCUS protocols which require assessment of 2 or more points on the lower limb veins[61]. 50% of patients with massive PE have DVT at the V-point, *i.e.* may be absent in 50%. Examining at one isolated point may not be as comprehensive as other protocols, but the author justifies this to avoid spending excessive time where there is low yield; and (4) Presence of DVT is used to "rule in" pulmonary embolism" as a cause of cardiac arrest[62]

AAA: Abdominal aortic aneurysm; AKI: Acute kidney injury; A4C: Apical 4 chamber; CCE: Critical care echocardiography; DVT: Deep vein thrombosis; ED: Emergency department; FAST: Focused assessment with sonography for trauma; IVC: Inferior vena cava; LR+: Positive likelihood ratio; LR-: Negative likelihood ratio; LV: Left ventricle; PE: Pulmonary embolism; PLAPS: Posterolateral alveolar and/or pleural syndrome; PLax: Parasternal long axis; POCUS: Point-of-care-ultrasound; RCT: Randomised controlled trial; RUSH: Rapid Ultrasound in Shock and Hypotension; RV: Right ventricle; VEXus: Venous Excess Ultrasonography Score; VTE: Venous thromboembolism; ICU: Intensive care unit.

deduction/calculation.

Another protocol is the Global Ultrasound Check for the Critically Ill (GUCCI) protocol, which integrates multiple protocols[14] and is organised based on 3 syndromes (acute respiratory failure, shock, cardiac arrest) and includes ultrasound-guided procedures. Compared to PIEPEAR, it has specific diagnostic questions to be answered, and has direct, specific management implications.

The ORACLE[15] protocol was designed for ICU patients with coronavirus disease 2019 (COVID-19) infections (O: Left ventricular functiOn, R: Right ventricular disease, A: vAlve disease, C: PeriCardium, L: Lung ultrasound, E: hEmodynamic parameters). It was designed such that POCUS is performed in a structured way while reducing additional staff (*e.g.* sonographers) exposure to infection. Images were acquired during ward rounds and offline measurements were done outside patient rooms.

FUTURE DIRECTIONS AND RESEARCH

POCUS has proven to be essential in triaging cases in the current COVID-19 pandemic, due to availability of relatively portable devices which are easy to disinfect. It reduces the logistical challenge of transporting patients to radiology suites or echocardiography units. The American Society of Echocardiographers (ASE) protocol combines cardiac, lung and vascular ultrasound and is an option for COVID-19 patients where cardiopulmonary disease requires evaluation. An added advantage of intensivists using POCUS is reducing exposure to other personnel and locations, permitting conservation of personal protective equipment[16].

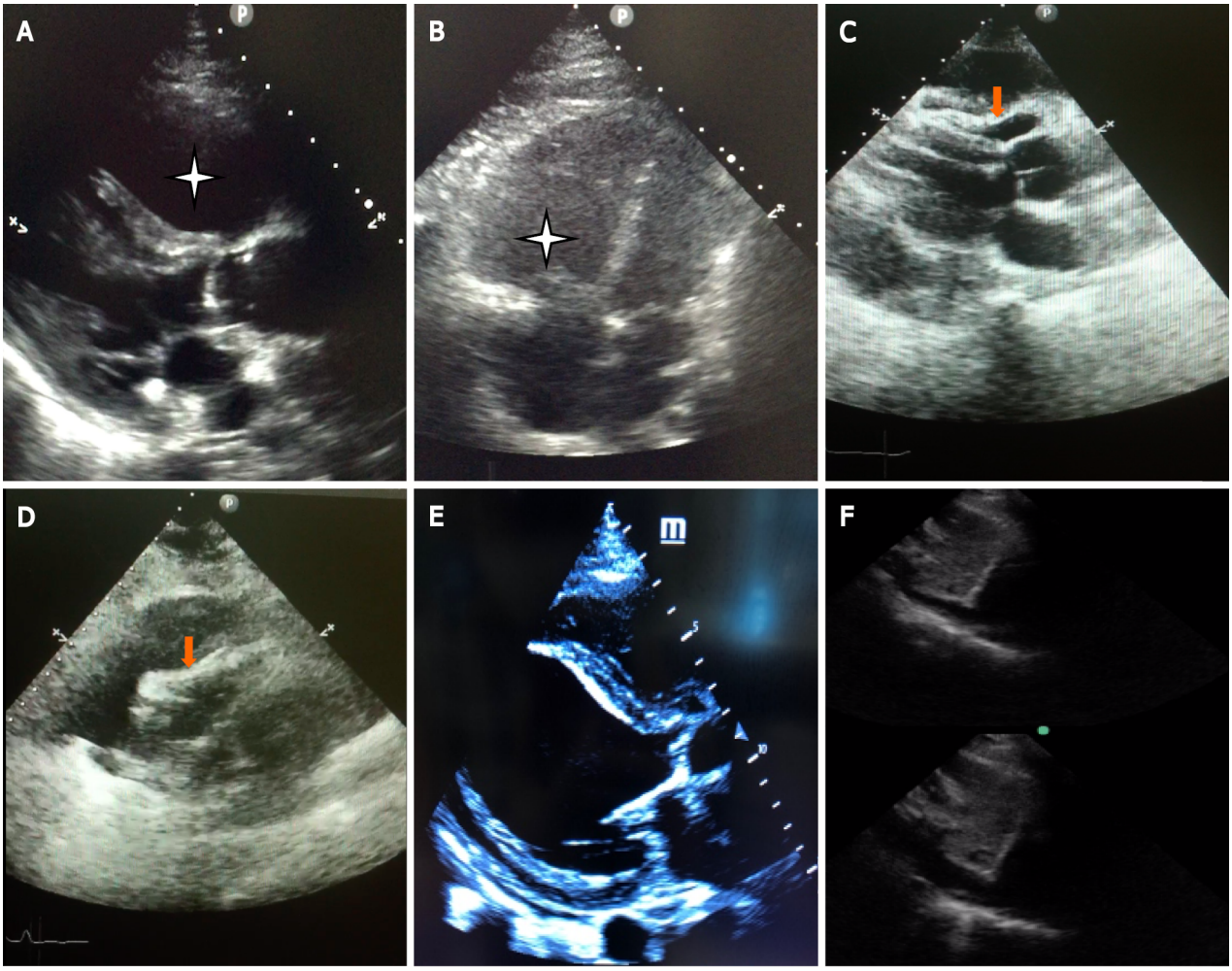

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Figure 1 Key features in basic critical care echocardiography. A: Dilated right ventricle [Parasternal long axis (PLAX)]; B: Dilated right ventricle (Apical 4 chamber view); C: Pericardial tamponade-Pericardial effusion with diastolic collapse of right ventricle (PLAX view); D: Pericardial tamponade–Pericardial effusion with systolic collapse of right atrium [subcostal long axis (SLAX) view]; E: Left ventricular dysfunction-minimal thickening and contraction of basal anteroseptal and inferolateral wall with severe hypokinesia (PLAX view); F: Inferior vena cava variation of > 50% with foreceful spontaneous respiration-"sniff test" (SLAX view).

Recently, POCUS has started to appear in the secondary survey of adult cardiac life support (ACLS) algorithm, and can be considered especially if it does not interfere with algorithm. This is to identify potentially reversible causes for cardiac arrest[17] or to detect return of spontaneous circulation (ROSC). Depending on the type of shock or history preceding cardiac arrest, targeted CCE may identify clues to the underlying cause such as a plethoric IVC and absence of lung sliding associated with tension pneumothorax, or small/normal ventricles and collapsed IVC due to hypovolemic shock. CCE may also identify tamponade, thrombus-in-transit, myocardial infarction as a cause of cardiac arrest[18]. However, the International Liaison Committee on Resuscitation (ILCOR) task force recommends that the individual performing POCUS is trained to minimise interruptions to chest compressions. With regards to prognostication, ILCOR currently suggests *against* the use of POCUS for prognostication during cardiopulmonary resuscitation due to weak evidence for any CCE findings in predicting outcomes. Although a single small randomized controlled trial (RCT) found no improvement in outcomes with use of cardiac ultrasound during cardiopulmonary resuscitation, this result is not definitive and more research is required[19].

There are other modalities of POCUS, although less commonly performed, that can be useful in the ICU. These include airway ultrasound, screening for deep vein thrombosis (DVT), diaphragm ultrasound and ultrasound to assess the optic nerve sheath diameter. Pre-procedural airway ultrasound improves safety prior to a percutaneous tracheostomy[20]. Diaphragm ultrasound can be used to detect diaphragm dysfunction with great accuracy[21]. Optic nerve sheath diameter ultrasound allows detection of raised intracranial pressure at the bedside and can be used for prognostication post cardiac arrest[22]. Evidence for utility of these POCUS modalities in changing patient-centred outcomes is still lacking. Additionally, the training requirements and learning trajectory remain areas for further development and research.

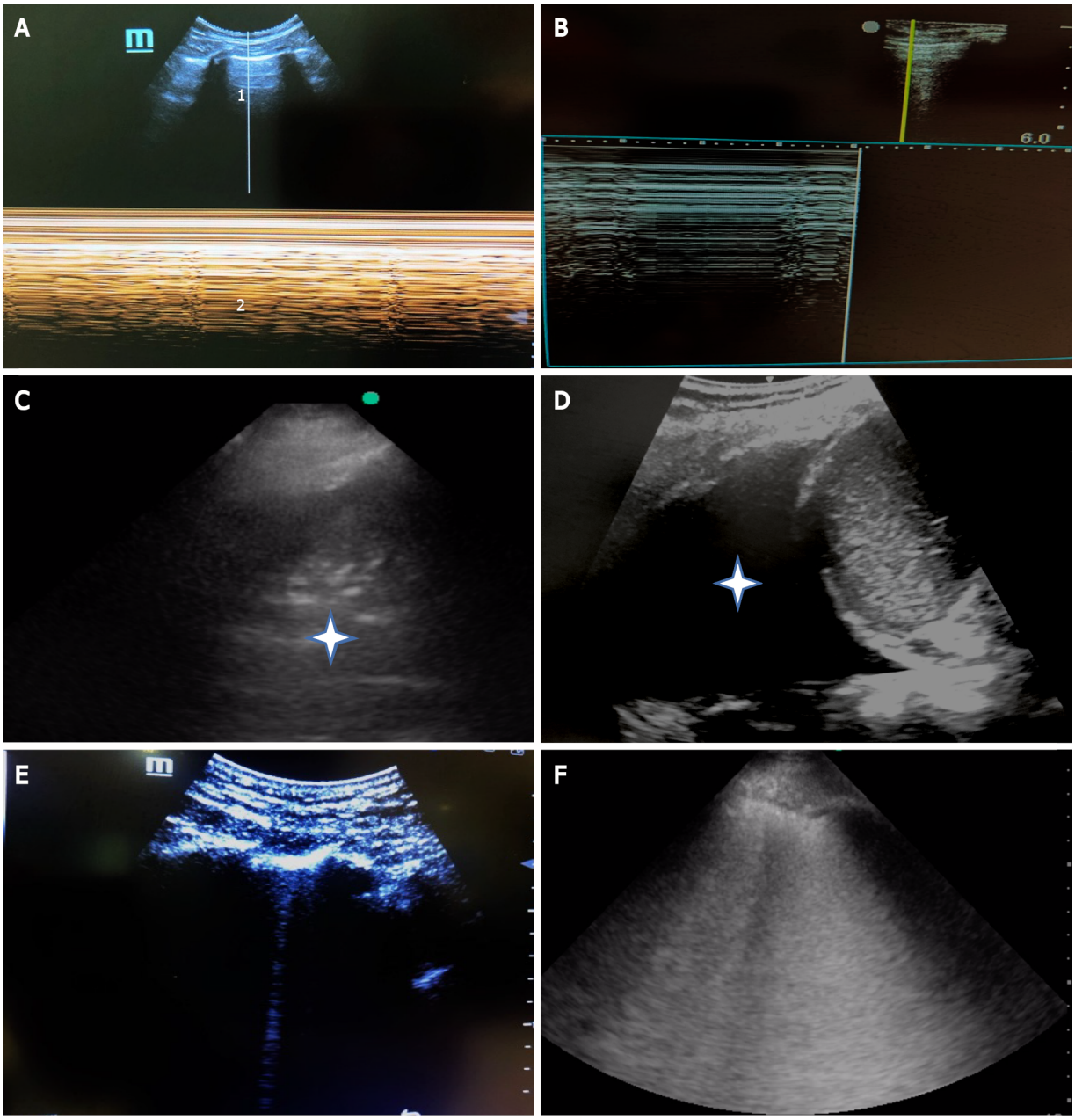

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Figure 2 Key features in basic lung ultrasound. A: M-mode lung ultrasound-normal a lines (1), and seashore sign (2); B: M-mode lung ultrasound-pneumothorax Bar code/stratosphere sign; C: Consolidation with air bronchograms (Asterisk); D: Pleural effusion (large); E: 1 single B line-normal; F: B profile, > 3 B lines (confluent)-pathological.

Currently, there has also been increasing interest in the use of artificial intelligence that provides real-time guidance for probe placement, aids acquisition of optimal images[23], and helps to reduce exposure of healthcare workers to highly infectious cases[24]. Such technology has also been used to help users identify anatomy and do measurements of cardiac function[23]. Whether these algorithms are able to replace a trained sonographer, improve scan durations and accuracy, and improve healthcare delivery or patient outcomes remain uncertain. Robot-assisted ultrasonography, with scans conducted by operators remotely, has also been described. These devices are 5G-powered with robotic arms manipulated by an operator in another room using a simulated robotic hand[25].

There are currently few studies evaluating if CCE or multi-organ POCUS has any effect on mortality, which might be confounded by many other factors. One retrospective study found that POCUS done on ED patients prior to interventions such as fluid boluses are associated with care delays and increased in-hospital mortality compared to critically ill patients with no POCUS[26]. Also, being a diagnostic and monitoring tool, the therapies given are variable depending on the clinician so it will be hard to link POCUS's utility directly with mortality. More studies are nonetheless needed to explore the effect of POCUS on patient-centred outcomes.

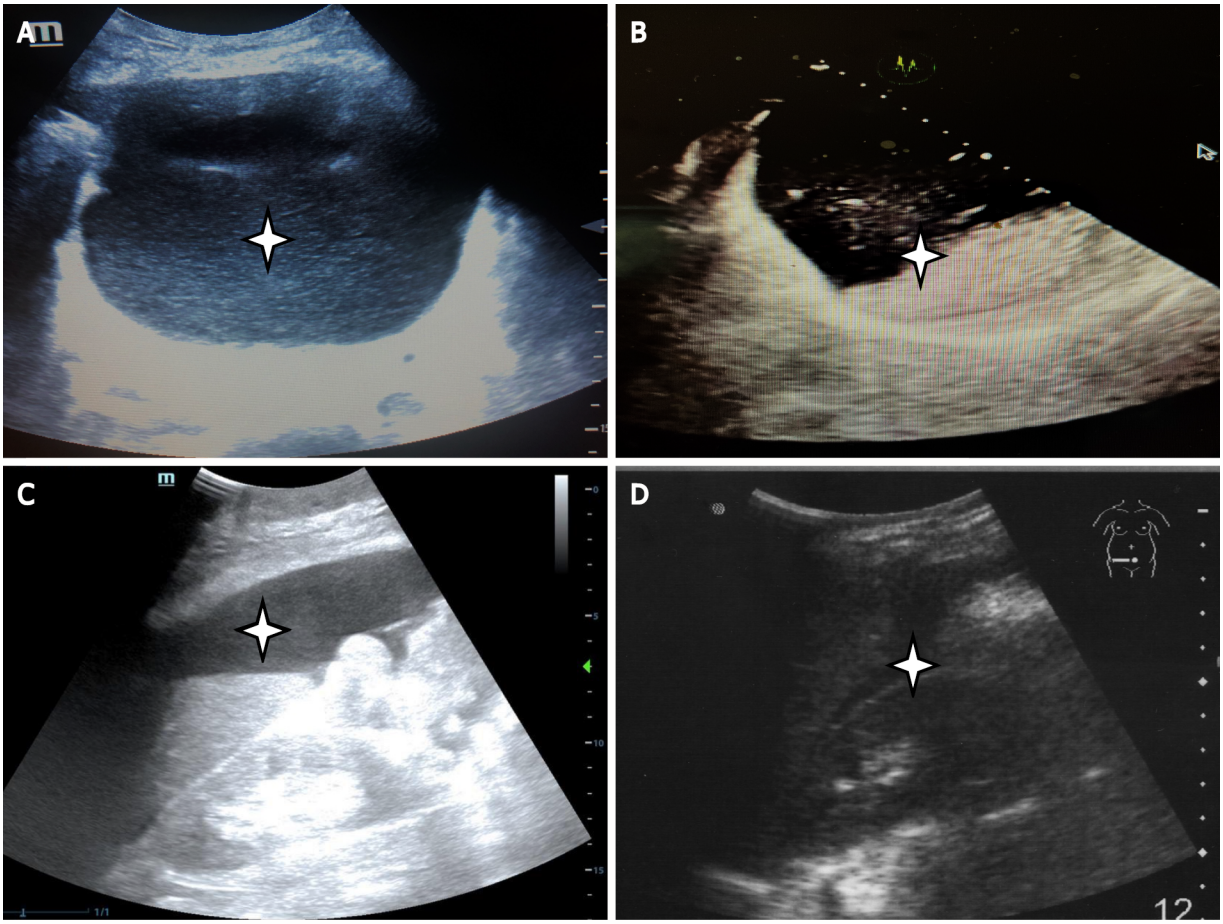

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Figure 3 Key features in abdominal ultrasound. A: Bladder overdistension due to acute retention of urine (Asterisk); B: Incomplete gastric emptying (presence of semi-digested food in the stomach, Asterisk), which will indicate need for rapid sequence induction for intubation; C: Ascites (Asterisk); D: Free fluid in the hepato-renal pouch. In cases with abdominal trauma, this indicates intra-peritoneal bleeding (Asterisk).

Given the multitude of POCUS protocols described, there will unlikely be head-to-head studies or standardization of included devices. Each medical unit needs to adopt POCUS protocols that are relevant to its clinical practice. This process must involve multi-disciplinary stakeholders and trainers so that it remains relevant during different parts of a patient's hospitalisation. This then leads to standardised curricula so that there can be quality assurance and reduction of inter-operator differences. More importantly, the systemic adoption of POCUS protocols can allow patient-centric outcomes to be studied. Needless to say, access to a point-of-care ultrasound machine is critical in adoption of POCUS on a regular basis. Given how each patient's critical illness, response to treatment and subsequent trajectory lie on a continuum, it would be useful if the unit has a picture archiving and communication system (PACS) to allow different healthcare providers involved in the care of the patient at different stages of the hospitalisation to compare the images. This system also can be used for POCUS education or competency assessment of POCUS learners by their supervisors. Even without a PACS system, this also can be achieved on ultrasound systems which allow storage of video or still clips. Such documentation may be increasingly important for oversight of POCUS practice, which is one of the concerns raised by the Joint Commission in naming POCUS as one of the top 10 health technology *hazards* in 2020[27].

Hand-held POCUS as an extension of physical exam (i.e. stethoscope) is becoming more popular. If POCUS is integrated with structured assessments such as ACLS (Advanced cardiac life support), advanced trauma life support (ATLS), CERTAIN (Checklist for Early Recognition and Treatment of Acute Illness and iNjury), and teams are equipped with ultrasound devices, it can provide additional information at the bedside which may change management. This includes right-siting of patients to the relevant medical disciplines (*e.g.* a dissecting aortic aneurysm sent to a hospital with cardiac surgery facilities), or pericardiocentesis in a patient who has shock due to tamponade. Pitfalls of incorporating POCUS to routine assessments include inappropriate use of this tool, misdiagnoses by inexperienced operators, excessive time taken, and distraction from clinical assessment and critical resuscitation tasks. POCUS was associated with longer pauses during cardio-pulmonary resuscitation especially comparing between ultrasound-fellowship trained *vs* non-fellowship trained operators[28]. If it becomes integrated

in such structured assessments, teams must be mindful of the caveats and ultrasound operators should be adequately trained, with safety mechanisms inbuilt (*e.g.* strict timekeeping for pulse-checks and interruptions in cardiopulmonary resuscitation). Such training may also need to focus on POCUS views which are more easily accessed during a resuscitation situation such as anterior lung, and subcostal echocardiography windows.

The quality of handheld devices is still lacking compared to traditional point-of-care- ultrasound systems, which may lead to poorer image quality or artefacts and misinterpretation. This is an area that is rapidly expanding with newer devices that are smaller coming out in the market, including probes that can be connected to smart devices, and recently artificial intelligence-integrated handheld devices.

CONCLUSION

Cardiac, lung and abdominal ultrasound should be part of the skillset of doctors managing critically ill patients. Being operator dependent, the accuracy of POCUS in detecting or excluding abnormalities may be influenced by the operator's experience. The influence of POCUS findings on treatment also depends on clinician experience. Several protocols combining different POCUS modalities have been described but the validity of these protocols in different settings still needs to be studied. There is a growing body of evidence describing the accuracy of POCUS applications, and with growing experience and competency one hopes that the accuracy will improve. POCUS should be considered a tool to confirm a diagnosis, as an extension of physical examination. More evidence is needed to recommend it as standard of care.

FOOTNOTES

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Country/Territory of origin: Singapore

ORCID number: Yie Hui Lau 0000-0003-1754-7515; Kay Choong See 0000-0003-2528-7282.

S-Editor: Fan JR
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ORIGINAL ARTICLE

Retrospective Study

Treatment with neurohormonal inhibitors and prognostic outcome in pulmonary arterial hypertension with risk factors for left heart disease

Riccardo Scagliola, Claudio Brunelli, Manrico Balbi

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Riccardo Scagliola, Claudio Brunelli, Manrico Balbi, Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Genova 16132, Genova, Italy

Corresponding author: Riccardo Scagliola, MD, Doctor, Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Largo R. Benzi No. 10, Genova 16132, Genova, Italy. risca88@live.it

Abstract

BACKGROUND

Despite major advances in pharmacologic treatment, patients with pulmonary arterial hypertension (PAH) still have a considerably reduced life expectancy. In this context, chronic hyperactivity of the neurohormonal axis has been shown to be detrimental in PAH, thus providing novel insights on the role of neurohormonal blockade as a potential therapeutic target.

AIM

To evaluate the application and prognostic effect of neurohormonal inhibitors (NEUi) in a single-center sample of patients with idiopathic PAH and risk factors for left heart disease.

METHODS

We analyzed data retrospectively collected from our register of right heart catheterizations performed consecutively from January 1, 2005 to October 31, 2018. Patients on beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or mineralocorticoid receptor antagonist at the time of right heart catheterization were classified as NEUi users and compared to NEUi non-recipients.

RESULTS

Complete data were available for 57 PAH subjects: 27 of those (47.4%) were taking at least one NEUi at the time of right heart catheterization and were compared with the remaining 36 NEUi non-recipients. NEUi users were older and had a higher cardiovascular risk profile compared to non-recipients. Additionally, NEUi non-users had a higher probability of dying during the course of follow-up than NEUi recipients (56.7% *vs* 25.9%, log-rank $P = 0.020$).

CONCLUSION
The above data highlighted a subgroup of patients with PAH and comorbidities for left heart disease in which NEUi use has shown to be associated with improved survival. Future prospective studies are needed to identify the most appropriate therapeutic strategies in this subset population.

Key Words: Pulmonary arterial hypertension; Left heart disease; Neurohormonal inhibitors; Prognostic outcome; Right heart catheterization; Pharmacological treatment

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Core Tip: In this observational study we underscored an increase in risk predictors for left heart disease among patients with idiopathic pulmonary arterial hypertension. Data were retrospectively collected from a single-center sample of patients with idiopathic pulmonary arterial hypertension who underwent right heart catheterization from January 1, 2005 to October 31, 2018. Among them, subjects treated with neurohormonal inhibitors showed a significantly better prognostic outcome during the course of follow-up as compared to neurohormonal inhibitor non-recipients.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a life-threatening cause of right ventricular failure, characterized by endothelial dysfunction and pulmonary vascular remodeling[1]. Despite major advances in pharmacologic treatment, patients with PAH still have a considerably reduced life expectancy. In this context, chronic hyperactivity of the neurohormonal axis has been shown to be detrimental in PAH, thus providing novel insights on the role of neurohormonal blockade as a potential therapeutic target [2]. To date, neurohormonal inhibitors (NEUi) are not currently labelled in PAH by contemporary guidelines, while they are used to treat PAH subjects with concomitant risk factors for left heart disease (LHD), for which they are instead scheduled for[3,4].

In recent years, further investigations have challenged the paradigm according to which PAH and pulmonary hypertension (PH) due to LHD are considered two separate pathophysiological entities. The AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial found a higher than expected prevalence of risk predictors for LHD among PAH patients[5]. In the same way, data from the COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Arterial Hypertension) and other registry reports showed a significant trend towards an increased age and a higher percentage of cardiovascular comorbidities at diagnosis of PAH, together with a weaker response to targeted PAH therapy[6,7]. So the emerging definition of 'atypical PAH' or 'PAH with comorbidities' has been coined to identify such a hybrid PH phenotype with a purely precapillary hemodynamic profile and risk predictors for LHD, in which a concealed post-capillary involvement may be supposed[8,9]. In this way, the favorable impact of NEUi in this subset population has been hypothesized, by targeting cardiovascular risk factors and hidden LHD.

MATERIALS AND METHODS

We evaluated retrospectively collected data of subjects who underwent right heart catheterization (RHC) in a single-center cohort followed in the Cardiology Unit of University Hospital San Martino in Genoa, Italy from January 1, 2005 up to October 31, 2018. Following the current European Society of Cardiology and European Respiratory Society guidelines for the diagnosis and treatment of pulmonary hypertension[3], PAH was defined hemodynamically by mean pulmonary arterial pressure ≥ 25 mmHg, together with pulmonary artery wedge pressure ≤ 15 mmHg and pulmonary vascular resistance > 3 Wood units, in the absence of other identifiable etiologies of precapillary PH.

We selected patients with idiopathic PAH and complete information about demographics, biochemical data and drug therapy at the time of RHC. Patients with PAH and associated clinical conditions, such as PH due to lung disease and/or hypoxia, chronic thromboembolic PH or PH related

to unclear or multifactorial mechanisms, were ruled out of the observational analysis. Subjects with a diagnosis of LHD (defined by instrumental signs of left ventricular systolic or diastolic dysfunction or left heart valvular disease) did not undergo hemodynamic assessment by RHC and were excluded from the study population, according to our guidelines recommended study protocol[3,10].

In order to rule out occult post-capillary PH in patients suspected of having PAH, rapid fluid administration of 500 mL 0.9% NaCl solution within 5 min (by pressure cuff, C-fusor 500, Smiths Medical, Minneapolis, MN, United States) was performed, and the response of pulmonary artery wedge pressure to shifts in volume status was recorded within 2 min after the fluid challenge[11,12].

Patients on beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or mineralocorticoid receptor antagonist at the time of RHC were classified as NEUi users and compared with NEUi non-recipients. Comparisons between NEUi users and NEUi non-users were performed in terms of demographics, cardiovascular risk factors, biochemical samples, hemodynamic parameters and prognostic outcome.

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the ethics committee of the Medical University of Genoa approved the protocol. Due to the retrospective design, written informed consent to participate in the study was not applicable.

Statistical analysis was carried out using the Statistica 13.1 software for Windows (StatSoft, Inc., Tulsa, OK, United States). Quantitative variables were expressed either as number (percentage of total) or mean ± standard deviation. The statistical significance of the results between the two groups was determined by means of either χ^2 test or *t*-test, as appropriate. Death from any cause was assessed by Kaplan-Meyer survival analysis. A P value < 0.05 was considered statistically significant.

RESULTS

Complete data were available for 57 patients affected by idiopathic PAH. The majority of them were female (64.9%), mean age was 63.6 ± 10.6 years and mean follow-up period was 4.2 ± 3.0 years. Mean pulmonary arterial pressure, pulmonary artery wedge pressure and pulmonary vascular resistance were 45.0 ± 14.9 mmHg, 11.0 ± 2.8 mmHg and 8.8 ± 5.0 Wood units, respectively. Twenty-seven patients (47.4%) were under treatment with at least one NEUi at the time of RHC and constituted the NEUi user group: 15 (26.3%) were taking angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and 12 (21.1%) beta-blockers, while 6 (10.5%) were taking mineralocorticoid receptor antagonists. The remaining 36 subjects of the study population belonged to the NEUi non-recipients.

The two groups were comparable in terms of PAH-specific drugs taken during the follow-up period, as well as of prognostic determinants for PAH provided by the current European guidelines, including World Health Organization functional class, 6-min walking distance, right atrial pressure, cardiac index and N-terminal pro-brain natriuretic peptide plasmatic levels (P = not significant). NEUi users were significantly older (67.6 ± 11.9 years *vs* 60.1 ± 14.5 years, P = 0.039), had a lower glomerular filtration rate (58.7 ± 22.7 mL/min/1.73 m^2 *vs* 73.7 ± 24.7 mL/min/1.73 m^2, P = 0.022), a higher body mass index (25.9 ± 4.4 *vs* 23.5 ± 3.5, P = 0.025), an increased prevalence of smoking habits (51.9% *vs* 20.0%, P = 0.025) and increased systemic arterial hypertension (74.1% *vs* 40.0%, P = 0.020) compared to non-recipients. Additionally, 5 NEUi recipients (18.5%) underwent coronary artery revascularization compared to NEUi non-users (P = 0.046). Baseline characteristics and statistical results are summarized in Table 1. NEUi non-users had a higher probability of dying during the course of follow-up than NEUi recipients (56.7% *vs* 25.9%, log-rank P = 0.020) (Figure 1).

DISCUSSION

The reported data detected a significantly higher cardiovascular risk profile in the study population, encountering more than 50% of subjects with arterial hypertension and more than 30% with smoking habits and dyslipidemia. Albeit limited by the retrospective nature of the investigation, the small size and the single-center origin of the sample examined, these findings are in agreement with the results from the AMBITION trial and substantiated by registry data supporting that PAH with cardiovascular comorbidities is a codified PH entity in clinical practice[5,7]. However, to date these data have not been acknowledged by the current international guidelines on PH, which still fail to consider patients with PAH and cardiovascular comorbidities as belonging to a defined clinical subset[3,13]. This lack in the current state of regard for PH has limited further speculation on the potential therapeutic effects of NEUi in these kinds of patients. In this regard, the analysis of the two patient populations studied herein showed a significantly higher cardiovascular risk profile for LHD among NEUi users, in whom a better prognostic outcome has been observed compared to NEUi non-recipients.

A plausible explanation to these observations comes from the beneficial effects of NEUi use on cardiovascular comorbidities, which tended to cluster in the NEUi users group acting mainly on systemic inflammation and microvascular circulation, with consequent worsening of right ventricular impairment and survival[14,15]. In the same line, data from the literature pointed out a plausible

Table 1 Baseline characteristics of the study population

Variable	NEUi non-users, *n* = 30	NEUi users, *n* = 27	*P*
Age in yr	60.1 ± 14.5	67.6 ± 11.9	0.039
Men/Women, *n* (%)	11 (36.7)/19 (63.3)	9 (33.3)/18 (66.7)	0.988
Follow-up in yr	4.0 ± 2.7	4.5 ± 3.3	0.504
Dead at follow-up, *n* (%)	17 (56.7)	7 (25.9)	0.038
BMI in kg/m^2	23.5 ± 3.5	25.9 ± 4.4	0.025
Arterial hypertension, *n* (%)	12 (40.0)	20 (74.1)	0.020
Smoking habits, *n* (%)	6 (20.0)	14 (51.9)	0.025
Dyslipidemia, *n* (%)	7 (23.3)	12 (44.4)	0.160
Diabetes mellitus, *n* (%)	2 (6.7)	5 (18.5)	0.339
Supraventricular arrhythmias, *n* (%)	4 (13.3)	7 (25.9)	0.386
Coronary artery disease, *n* (%)	0 (0)	5 (18.5)	0.046
eGFR in mL/min/1.73 m^2 [CKD-EPI]	73.7 ± 24.7	58.7 ± 22.7	0.022
WHO-FC	2.2 ± 0.76	2.3 ± 0.47	0.572
6MWD in m	383.9 ± 129.7	374.3 ± 145.1	0.845
NT-proBNP in ng/mL	714.9 ± 692.4	808.7 ± 617.9	0.593
Systolic PAP in mmHg	74.7 ± 26.3	71.0 ± 21.3	0.569
Diastolic PAP in mmHg	27.5 ± 11.6	26.3 ± 9.6	0.681
Mean PAP in mmHg	46.2 ± 16.1	43.6 ± 13.6	0.509
Right atrial pressure in mmHg	8.3 ± 3.9	10.5 ± 5.0	0.063
PAWP in mmHg	10.5 ± 2.9	11.7 ± 2.5	0.105
PVR in Wood unit	9.0 ± 5.4	8.6 ± 4.6	0.789
Cardiac index in L/min/m^2	2.6 ± 0.9	2.4 ± 0.6	0.258

BMI: Body mass index; NEUi: Neurohormonal inhibitors; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: Estimated glomerular filtration rate; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAP: Pulmonary arterial pressure; PAWP: Pulmonary artery wedge pressure; PVR: Pulmonary vascular resistance; 6MWD: 6-min walking distance; WHO-FC: World Health Organization functional class.

overlap between idiopathic PAH and PH due to LHD in terms of pathophysiologic mechanisms, prognostic outcomes and response to targeted PAH-specific treatment[11,14]. In the analysis conducted by Obokata *et al*[16], the activation of the endothelin signaling pathway seemed to contribute to right ventricular functional impairment in subjects with heart failure with preserved ejection fraction, while endothelin-1 is also historically known for its pathogenic role in developing PAH by pulmonary vasoconstriction, smooth muscle cell proliferation and pulmonary vascular remodeling.

Several studies emphasized a proposed paradigm whereby metabolic syndrome and cardiovascular comorbidities could reinforce PH in patients with LHD by exploiting molecular pathways actively involved in developing PAH, like a deranged interplay between decreased microvascular nitric oxide availability and enhanced endothelin expression[17-20]. Therefore, the close relationship between these two PH phenotypes raised the hypothesis of a potential continuum disease, in which PAH with risk factor for LHD lies in-between. For these reasons, it is possible to assume that the better prognostic outcome observed in NEUi recipients of our study population could also be intrinsically related to an intermediate pathophysiologic standpoint in the spectrum of disease (phenotypically closer to PH due to LHD albeit with a hemodynamic profile comparable with precapillary PH) rather than solely ascribed to the therapeutic properties of neurohormonal axis blockers on cardiovascular comorbidities.

Finally, considering the aforementioned upregulation of the neurohormonal axis in PAH and its deleterious properties on worsening right heart failure in the long-run, a direct favorable implication of NEUi on right ventricular function and pulmonary circulation in this study population may be also taken into account[2,21].

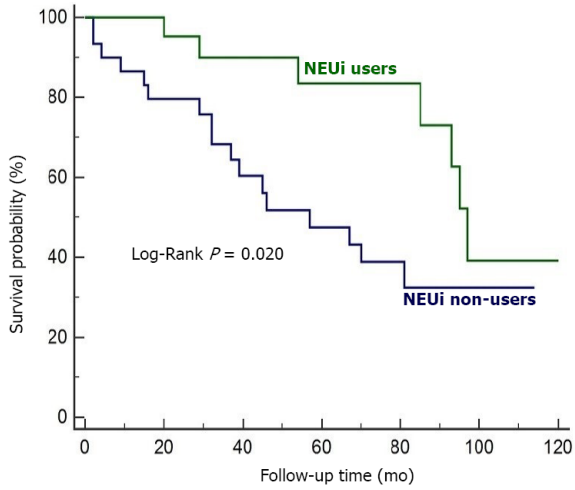

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Figure 1 Survival curves of the study population according to neurohormonal inhibitors users or non-users. NEUi: Neurohormonal inhibitors.

CONCLUSION

In conclusion, our data highlighted a codified subset of patients with PAH and a comorbidity profile for LHD, lying between the extremes of a pathophysiological continuum, in which NEUi use has been shown to be associated with a better prognostic outcome. Further investigation is required to define the proper pharmacological treatment in patients with PAH and hidden LHD.

ARTICLE HIGHLIGHTS

Research background

Despite new insights in pharmacological treatment, patents with pulmonary arterial hypertension (PAH) still have a considerably reduced life expectancy.

Research motivation

Chronic hyperactivity of the neurohormonal axis has been shown to be detrimental in PAH, thus providing novel insights on the role of neurohormonal inhibitors (NEUi) as a new potential therapeutic target.

Research objectives

To assess the use and prognostic impact of NEUi in a single-center cohort of subjects with idiopathic PAH and risk factors for left heart disease.

Research methods

This was a single-center, retrospective observational study, involving 57 subjects with idiopathic PAH, confirmed by right heart catheterization. Patients on beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or mineralocorticoid receptor antagonist at the time of right heart catheterization were classified as NEUi users and compared to NEUi non-recipients.

Research results

NEUi users were significantly older (67.6 ± 11.9 years *vs* 60.1 ± 14.5 years, $P = 0.039$), had a higher body mass index (25.9 ± 4.4 *vs* 23.5 ± 3.5, $P = 0.025$), a lower estimated glomerular filtration rate (58.7 ± 22.7 mL/min/1.73 m^2 *vs* 73.7 ± 24.7 mL/min/1.73 m^2, $P = 0.022$) and more frequent systemic arterial hypertension (74.1% *vs* 40.0%, $P = 0.020$) and smoking habits (51.9% *vs* 20.0%, $P = 0.025$) compared to non-recipients. Mortality rate was significantly higher among NEUi non-users than in NEUi users (56.7% *vs* 25.9%, $P = 0.038$). NEUi non-users were more likely to die over the course of follow-up (log-rank $P = 0.020$).

Research conclusions

Our analysis highlighted a subset of patients with PAH and cardiovascular comorbidities in which NEUi use has been shown to be associated with improved survival.

Research perspectives

Future prospective studies are needed to identify the most appropriate therapeutic strategies in this subset population.

FOOTNOTES

Author contributions: Scagliola R and Balbi M contributed to the conception and design of the study and acquired and interpreted the data; Brunelli C and Balbi M analyzed the data; Scagliola R drafted the manuscript; All authors contributed equally to the critical revision, editing and approval of the final version of the manuscript.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board committee at the University of Genoa, Italy.

Informed consent statement: Due to the retrospective design, written informed consent to participate in the study was not applicable.

Conflict-of-interest statement: None to be declared.

Data sharing statement: The present data are anonymized, with no risk of identification.

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Country/Territory of origin: Italy

ORCID number: Riccardo Scagliola 0000-0002-5439-3300; Claudio Brunelli 0000-0002-1688-4467; Manrico Balbi 0000-0002-4604-3204.

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ORIGINAL ARTICLE

Retrospective Study

Retrospective analysis of aspirin's role in the severity of COVID-19 pneumonia

Maya Gogtay, Yuvaraj Singh, Asha Bullappa, Jeffrey Scott

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Maya Gogtay, Yuvaraj Singh, Department of Internal Medicine, Saint Vincent Hospital, Worcester, MA 01604, United States

Asha Bullappa, Community Medicine and Biostatistics, SS Institute of Medical Sciences, Davangere 577003, Karnataka, India

Jeffrey Scott, Department of Critical Care Medicine and Pulmonology, Reliant medical group-Saint Vincent Hospital, Worcester, MA 01604, United States

Corresponding author: Maya Gogtay, MD, Doctor, Department of Internal Medicine, Saint Vincent Hospital, 123 Summer street, Worcester, MA 01604, United States.
drgogtay@gmail.com

Abstract

BACKGROUND

Since December 2019, an outbreak of pneumonia caused by severe acute respiratory syndrome - coronavirus-2 (SARS-CoV-2) has led to a life-threatening ongoing pandemic worldwide. A retrospective study by Chow *et al* showed aspirin use was associated with decreased intensive care unit (ICU) admissions in hospitalized coronavirus disease 2019 (COVID-19) patients. Recently, the RECOVERY TRIAL showed no associated reductions in the 28-d mortality or the progression to mechanical ventilation of such patients. With these conflicting findings, our study was aimed at evaluating the impact of daily aspirin intake on the outcome of COVID-19 patients.

AIM

To study was aimed at evaluating the impact of daily aspirin intake on the outcome of COVID-19 patients.

METHODS

This retrospective cohort study was conducted on 125 COVID-19 positive patients. Subgroup analysis to evaluate the association of demographics and comorbidities was undertaken. The impact of chronic aspirin use was assessed on the survival outcomes, need for mechanical ventilation, and progression to ICU. Variables were evaluated using the chi-square test and multinomial logistic regression analysis.

RESULTS

125 patients were studied, 30.40% were on daily aspirin, and 69.60% were not. Cross-tabulation of the clinical parameters showed that hypertension (P = 0.004), hyperlipidemia (0.016), and diabetes mellitus (P = 0.022) were significantly associated with aspirin intake. Regression analysis for progression to the ICU, need for mechanical ventilation and survival outcomes against daily aspirin intake showed no statistical significance.

CONCLUSION

Our study suggests that daily aspirin intake has no protective impact on COVID-19 illness-associated survival outcomes, mechanical ventilation, or progression to ICU level of care.

Key Words: COVID-19; Aspirin; Intensive care unit progression; Antiplatelet; Hyper-coagulability; Anti-inflammatory

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Core Tip: Our study suggests that aspirin has no beneficial effects with regards to progression to intensive care unit (ICU) from the medical floors in coronavirus disease 2019 (COVID-19) positive patients. This study was conducted on the patients presenting during the early phase of the pandemic when there was little evidence on the most beneficial modality of treatment. Over the last 2 years we have learned about the pro-thrombotic nature of COVID-19. Since aspirin is a widely dispensed medication in our adult population, we questioned if its chronic use could have a preventive effect on ICU progression of patients admitted to the medical floors. However, our data analysis suggests that there was no such protective effect.

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INTRODUCTION

Since December 2019, an outbreak of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a life-threatening ongoing pandemic worldwide[1]. Several nonsteroidal anti-inflammatory drugs (NSAIDs) have been used in patients with SARS-CoV-2 infection, but many remain controversial effects on the disease[2]. Aspirin (acetylsalicylic acid), a popular medicine, exhibits a variety of effects, including alleviating anti-inflammatory response, reducing fever and pain, and blocking viral propagation of RNA viruses (*e.g.*, influenza virus and hepatic C virus)[3]. Moreover, coagulopathy plays a central role in the patho-mechanism of coronavirus disease 2019 (COVID-19), which leads to end-organ complications and death[4-6]. COVID-19 has been linked with increased thromboembolic complications such as venous thro-mboembolism, stroke, and myocardial infarction[7-10]. Aspirin is potentially beneficial in patients with COVID-19 due to its antithrombotic nature[11]. Aspirin primarily acts by inhibiting platelet function through irreversible inhibition of cyclo-oxygenase (COX) activity. Low-dose aspirin inhibits COX-1, resulting in reduced thromboxane A2 synthesis which prevents platelet activation and aggregation[12,13]. In a retrospective study by Chow *et al*[14], it was found that aspirin use may be associated with improved outcomes, reduced rates of mechanical ventilation, and decreased intensive care unit (ICU) admissions in hospitalized COVID-19 patients. Given the encouraging findings, the world's largest randomized controlled open-label trial was performed using approximately 15000 patients in the UK (RECOVERY TRIAL)[15]. The patients in the study were allocated to receive aspirin after diagnosis of COVID-19 during in-hospital admission, and the results showed no associated reductions in the 28-d mortality or the progression to mechanical ventilation of such patients. With the above conflicting findings, the present study was designed to evaluate the impact of daily aspirin intake prior to hospitalization on the rate of COVID-19 positive patients' progression to the ICU.

MATERIALS AND METHODS

This single-center retrospective cohort study was conducted on patients that tested COVID-19 positive and were admitted between March and April 2020. IRB approval was obtained before initiating the

study. Patient data including demographic information, history of comorbidities like hypertension, hyperlipidemia and diabetes mellitus, medication use like aspirin, P2Y12 inhibitor, warfarin and NOACs, clinical characteristics, and clinical outcomes were retrieved from the hospital database based on the following inclusion and exclusion criteria.

Inclusion criteria

COVID-19 positive in-patients. Adults aged 18 years and older.

Exclusion criteria

Patients with incomplete medical records. Pregnant women and patients aged 17 years and younger.

All the collected data were stored securely in a password-protected computer, and any paper records were securely stored. Only the approved study team had access to data.

Based on intensive retrospective chart review and recording the baseline characteristics of the patients, they were divided into two cohorts. The first cohort consisted of patients taking daily aspirin of at least 81 mg, and those who were not taking daily aspirin were placed in the second cohort. The patients were on chronic daily aspirin prior to contracting COVID-19 and hospitalization. Aspirin intake was recorded as per their pre-admission medication history. For both the cohorts, we calculated various outcomes, which included the percentage of patients progressing to the ICU, percentage of patients requiring oxygen supplementation, and percentage of patients requiring mechanical ventilation. We also calculated survival outcomes for the two groups. Additionally, subgroup analysis was undertaken by comparing various age groups and gender. All the statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 21.0; IBM Corp, Armonk, NY, United States). Categorical variables were analyzed using the chi-square test; $P < 0.05$ was considered statistically significant. A multinomial logistic regression analysis was done to study the relationship between various outcomes (ICU admission, intubation rate, and survival rate) and multiple independent variables like the use of aspirin, warfarin, NOACs, P2Y12 inhibitors, and comorbidities like hypertension and diabetes mellitus.

RESULTS

One hundred and twenty-five patients met our inclusion criteria and were stratified for further analysis. Out of them, 38 (30.40%) patients were on daily aspirin, and 87 (69.60%) were not. The majority of the 125 study subjects, *i.e*, 25.6% of the study subjects, belonged to the age group of 76-85 years, followed by 20.8% in the 56-65 age group. 19.2%, 15.2%, 12%, 4%, and 3.2% of study subjects belonged to above 85, 66-75, 46-55, 36-45, and 24-35 years of age respectively. The chi-square test showed a significant (P = 0.016) difference in age groups of study subjects taking daily aspirin as shown in Figure 1.

Amongst the 125 patients, we found that 41.6% were males not taking daily aspirin, 28% were females not taking aspirin, 17.6% were women taking daily aspirin, 12.8% were males on daily aspirin (P = 0.068), as depicted in Figure 2.

For those on daily aspirin, 32 (84.21%), 30 (78.94%), and 18 (47.36%) subjects had significant comorbidities like hypertension, hyperlipidemia and diabetes mellitus, respectively. Cross-tabulation of the clinical parameters of study subjects showed that hypertension (P = 0.004), hyperlipidemia (P = 0.016), diabetes mellitus (P = 0.022), were significantly associated with aspirin intake (Table 1).

In terms of outcomes, 9 (23.68%) patients were on aspirin *vs* 38 (43.6%) not on aspirin progressed to requiring ICU level of care (P = 0.034) as depicted in Figure 3. 5 (13.15%) on aspirin required mechanical ventilation contrary to 21 (24.13%) not on aspirin (P = 0.16). 36 (94.73%) of aspirin users required supplemental oxygen *vs* 73 (83.9%) not on aspirin (P = 0.096). 26 (68.5%) on aspirin survived *vs* 66 (75.8%), not on aspirin (P = 0.38) as depicted in Table 1.

A multinomial logistic regression analysis was further used to predict the categorical placement of each independent variable (aspirin, warfarin, NOACs, P2Y12 inhibitors, hypertension and diabetes mellitus) against the dependent variables: (1) Progression to ICU (Table 2); (2) Need for mechanical ventilation (Table 3); and (3) Survival outcomes (Table 4).

The analysis showed that aspirin users had an odds ratio of 0.367 (P = 0.03, CI: 0.378-2.26), predicting the odds of a patient taking aspirin progressing to the ICU is 0.3677 higher than those not being on aspirin if all the other predictor variables were held constant as represented in Table 2, though not significant.

The odds ratio of warfarin was 1.466 (P = 0.60, CI: 0.179-3.701) higher risk of ICU transfer than those not on warfarin. NOACs users had an odds ratio of 0.8522 (P = 0.79, CI: 0.229-2.520) and P2Y12 inhibitors were 2.998 (P = 0.22, CI: 0.141-5.144). Similarly, comorbidities (hypertension and diabetes mellitus) showed no significant impact on ICU admissions.

Other dependent variables like the need for mechanical ventilation and survival outcomes of the patients were also analyzed using the same independent variables with no significant association as in Table 3 and Table 4, respectively.

Table 1 Distribution of clinical parameters based on aspirin intake

Patient characteristics		Aspirin		Total (n = 125)	χ^2 value	P value
		Taking (n = 38)	Not taking aspirin (n = 87)			
Warfarin	Yes	4	5	9	0.90	0.34
	Percentage (%)	3.2	4.0	7.2		
	No	34	82	116		
	Percentage (%)	27.2	65.6	92.8		
Direct oral anticoagulants (NOAC)	Yes	6	9	15	0.74	0.38
	Percentage (%)	4.8	7.2	12.0		
	No	32	78	110		
	Percentage (%)	25.6	62.4	88.0		
P2Y12 inhibitors	Yes	1	5	6	0.56	0.45
	Percentage (%)	0.8	4.0	4.8		
	No	37	82	119		
	Percentage (%)	29.6	65.6	95.2		
Hypertension	Present	32	50	82	8.38	0.004[a]
	Percentage (%)	84.2	57.4	65.6		
	Absent	6	37	43		
	Percentage (%)	15.78	42.5	34.4		
Hyperlipidemia	Present	30	49	79	5.82	0.016[a]
	Percentage (%)	78.9	56.32	63.2		
	Absent	8	38	46		
	Percentage (%)	21	43.6	36.8		
Diabetes Mellitus	Present	18	23	41	5.25	0.022[a]
	Percentage (%)	47.36	26.4	32.8		
	Absent	20	64	84		
	Percentage (%)	52.6	73.5	67.2		
Immunosuppression	Yes	3	4	7	0.54	0.46
	Percentage (%)	7.8	4.5	5.6		
	No	35	83	118		
	Percentage (%)	92.1	95.4	94.4		
ICU admission	Admitted to ICU	9	38	47	4.50	0.034[a]
	Percentage (%)	23.6	43.67	37.6		
	Remained on medical floors	29	49	78		
	Percentage (%)	90.6	56.3	62.4		
Intubation	Yes	5	21	26	1.93	0.16
	Percentage (%)	13.1	24.1	20.8		
	No	33	66	99		
	Percentage (%)	86.8	75.8	79.2		
Outcome (survival)	Survived	26	66	92	0.75	0.38
	Percentage (%)	68.4	75.8	73.6		
	Died	12	21	33		
	Percentage (%)	31.5	24.1	26.4		

PE/DVT	Present	2	1	3	1.91	0.16
	Percentage (%)	5.2	1.1	2.4		
	Absent	36	86	122		
	Percentage (%)	94.7	98.8	97.6		
Oxygen use	Present	36	73	109	2.77	0.096
	Percentage (%)	94.7	83.9	87.2		
	Absent	2	14	16		
	Percentage (%)	5.2	16	12.8		

[a]$P \leq 0.05$.

Table 2 Logistic regression result for progression to the intensive care unit

Characteristics	Regression coefficients	Standard error	χ^2 (wald)	*P* value	Odds ratio	95%CI
Intercept	-0.45044	0.332171	1.838826	0.175089	0.637351	
Aspirin	-1.00047	0.46281	4.67307	0.030639	0.367707	0.365575-2.269164
Warfarin	0.382791	0.733339	0.272467	0.601681	1.466372	0.179321-3.701697
NOAC's	-0.15984	0.616872	0.067143	0.795543	0.852277	0.22984-2.520831
P2Y12 inhibitors	1.098044	0.908435	1.461005	0.22677	2.998296	0.142169-5.14458
HTN	0.213851	0.424561	0.253712	0.614473	1.238438	0.259028-1.790559
DM	0.018183	0.432623	0.001767	0.966474	1.01835	0.187667-1.05208

NOAC's: Novel oral anticoagulants; HTN: Hypertension; DM: Diabetes mellitus.

Table 3 Logistic regression results for need for mechanical ventilation

Characteristics	Regression coefficients	Standard error	χ^2 (wald)	*P* value	Odds ratio	95%CI
Intercept	-1.22056	0.389142	9.83799	0.001709	0.295063	
Aspirin	-0.83593	0.566163	2.179995	0.139815	0.433472	0.142903-1.31486
Warfarin	0.1583	0.859459	0.033924	0.853868	1.171517	0.217358-6.314246
NOACs	-0.54597	0.812938	0.451048	0.501838	0.57928	0.117737-2.850114
P2Y12 inhibitors	-0.42413	1.139528	0.138534	0.709742	0.654336	0.070118-6.106168
HTN	0.22629	0.500756	0.20421	0.651344	1.253939	0.469929-3.345963
DM	0.020291	0.510762	0.001578	0.968312	1.020498	0.375017-2.776985

NOAC's: Novel oral anticoagulants; HTN: Hypertension; DM: Diabetes mellitus.

DISCUSSION

In a multi-center cohort study on COVID-19 patients by Chow *et al*[14], aspirin use was independently associated with a lower risk of mechanical ventilation, ICU admission, and in-hospital mortality. Given aspirin's wide inexpensive use, it could be the answer we are looking for especially in low-income countries where expensive immunomodulators aren't readily available[14]. But a recent randomized controlled, open-label trial - RECOVERY, compared multiple treatments, including 150 mg aspirin once daily. They found that in hospitalized COVID-19 patients, aspirin was not associated with reductions in 28-d mortality or the risk of progressing to invasive mechanical ventilation or death but was associated with a slight increase in the rate of being discharged alive within 28 d[15]. Given the conflicting nature of recent studies, we sought to evaluate the effect of daily aspirin intake on clinical outcomes in hospitalized patients with COVID-19 and its impact on the rate of COVID-19 positive patient's progression to ICU.

Table 4 Logistic regression results for survival outcomes

Characteristics	Regression coefficients	Standard error	χ^2 (wald)	*P* value	Odds ratio	95%CI
Intercept	1.689138	0.422469	15.98599	6.38E-05	5.41481	
Aspirin	-0.07596	0.456833	0.027651	0.867932	0.926849	0.378575-2.269164
Warfarin	-0.20489	0.772302	0.070384	0.790778	0.814735	0.179321-3.701697
NOACs	-0.27293	0.610988	0.199538	0.655094	0.761148	0.229824-2.520831
P2Y12 inhibitors	-0.1564	0.915497	0.029184	0.864355	0.855219	0.142169-5.14458
HTN	-0.38415	0.49321	0.606636	0.436057	0.681032	01.790559
DM	-0.81116	0.439766	3.402248	0.065108	0.444344	1.05208

NOAC's: Novel oral anticoagulants; HTN: Hypertension; DM: Diabetes mellitus.

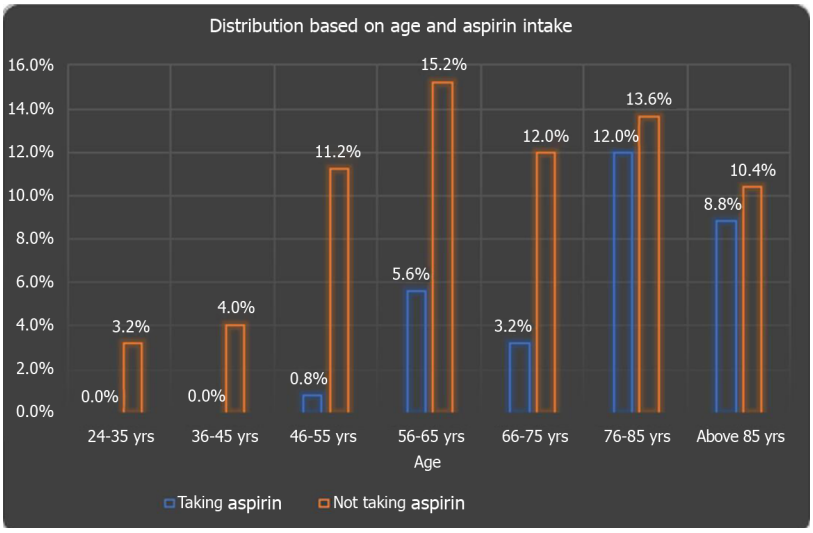

Figure 1 Distribution of study population based on age and aspirin intake (chi-square value of 15.66, *P* value = 0.016).

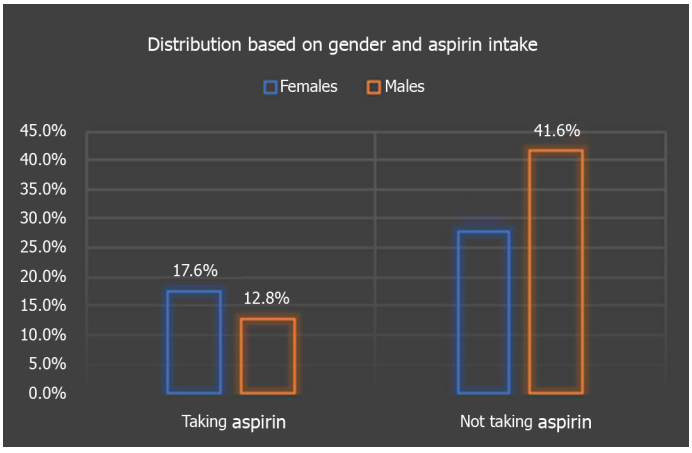

Figure 2 Distribution of study subjects based on gender and aspirin intake (χ^2 value = 3.32, *P* value = 0.068).

Our study analyzed 125 patients, of which 38 patients were on daily aspirin use, with a minimum dose of 81 mg. The study showed a significant association in variables such as age groups, hypertension, hyperlipidemia, and diabetes mellitus. This insinuated that our aspirin patients were older, and most of them had significant comorbidities, putting them at risk of severe COVID-19 illness.

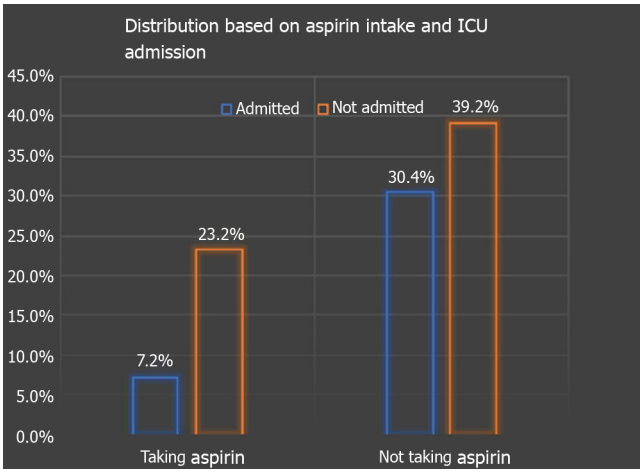

Figure 3 Distribution of study subjects based on aspirin and intensive care unit admission (χ^2 = 4.50, *P* value = 0.034). ICU: Intensive care unit.

At first glance, aspirin showed a possible protective role in progression to ICU on chi-square analysis. It failed to reach significance in multinomial logistic regression analysis. Furthermore, in terms of mortality, patients on aspirin had a higher mortality rate of 32% as compared to only 25% for non-aspirin users. This could be explained by the fact that patients on aspirin were older and had more comorbidities.

Hence, we conclude that aspirin shows no protective role for COVID-19 patients in terms of progression to ICU, survival outcome, and use of mechanical ventilation. Our findings concurred with the results of the RECOVERY trial[15].

Furthermore, bleeding risk is a potential adverse event while on aspirin. In the RECOVERY TRIAL, the incidence of major bleeding events was higher in the aspirin group (1.6% *vs* 1.0%; absolute difference 0.6%, SE: 0.2%). There were 18 reports of serious adverse events believed related to aspirin, all due to hemorrhagic in nature[15]. Even though we did not assess bleeding risk, this is a serious adverse event to bear in mind.

The advantage of our study is that it was conducted on the cohort of patients that presented at our hospital during the initial phase of the COVID-19 pandemic back in March of 2020. At that time, the use of corticosteroids and remdesivir were not established as the standard of care, and hence our study is not confounded by the effects of these medications.

The limitations of our study include a modest sample size and a retrospective - observational analysis, which limits generalizability and adjustment for confounding variables. We did not collect data on other concomitant medications - like statins or ACEI/ARBs, as most patients on aspirin are usually on the above, due to guideline-directed medical therapy for cardiovascular diseases, which could confound results. Some of our patients had their daily aspirin use discontinued after admission due to inability to tolerate enteral feeds, new bleeding complications, or being started on other anticoagulants owing to COVID-19 complications.

CONCLUSION

Our study suggests that aspirin does not have beneficial effects regarding progression to ICU from the medical floors in COVID-19 positive patients. Furthermore, it showed no statistically significant impact in reducing rates of mechanical ventilation, oxygen requirement, or decreasing mortality in patients.

ARTICLE HIGHLIGHTS

Research background

In a retrospective study by Chow *et al*, it was found that aspirin use may be associated with improved outcomes, reduced rates of mechanical ventilation, and decreased intensive care unit (ICU) admissions in hospitalized coronavirus disease 2019 (COVID-19) patients. Given the encouraging findings, the world's largest randomized controlled open-label trial was performed using approximately 15000 patients in the UK (RECOVERY TRIAL). The patients in the study were allocated to receive aspirin after diagnosis of COVID-19 during in-hospital admission, and the results showed no associated reductions in the 28-d mortality or the progression to mechanical ventilation of such patients. With the above

conflicting findings, the present study was designed to evaluate the impact of daily aspirin intake prior to hospitalization on the rate of COVID-19 positive patients' progression to the ICU.

Research motivation

With the never ending COVID-19 pandemic, it is imperative we find ways to keep patients out of the ICU. We have learnt that COVID-19 illness has major thrombotic and inflammatory effects. Aspirin would seem like an ideal choice to curb these effects. With this in mind, we conducted our study. But surprisingly we found that aspirin has no beneficial effects when it comes to preventing severe COVID-19 illness like ICU admissions. We postulate that patients taking aspirin were also older and had significant comorbidities, putting them at high risk for severe COVID-19. Furthermore, this study was carried out back when the most effective treatment modalities like steroids and remdesivir were not used. Hence, we conclude that aspirin's antiviral, anti-inflammatory and anti-thrombotic properties may not be strong enough to combat the COVID-19 illness.

Research objectives

Present study was designed to evaluate the impact of daily aspirin intake prior to hospitalization on the rate of COVID-19 positive patients' progression to the ICU.

Research methods

The idea of using the below methods were modeled after the study by Chow *et al* and the recovery trial on Aspirin in patients admitted to the hospital with COVID-19. Research methods adopted were the following: (1) Categorical variables, such as demographic information, comorbidities, receipt of investigational therapeutics, type of oxygen support, mechanical ventilation need, and outcomes, were reported as the number and percentage of patients and were compared between groups using the χ^2 test. P values < 0.05 were considered statistically significant; and (2) Multinomial logistic regression analysis to control for interplay of confounding from other anti-coagulation agents.

Research results

Our study analyzed 125 patients, of which 38 patients were on daily aspirin use, with a minimum dose of 81 mg. The study showed a significant association of aspirin with variables such as age groups, hypertension, hyperlipidemia, and diabetes mellitus. This insinuated that our aspirin patients were older, and most of them had significant comorbidities, putting them at risk of severe COVID-19 illness. At first glance, aspirin showed a possible protective role in progression to ICU on chi-square analysis. It failed to reach significance in multinomial logistic regression analysis. Furthermore, in terms of mortality, patients on aspirin had a higher mortality rate of 32% as compared to only 25% for non-aspirin users. This could be explained by the fact that patients on aspirin were older and had more comorbidities.

Research conclusions

We conclude that aspirin shows no protective role for COVID-19 patients in terms of progression to ICU, survival outcome, and use of mechanical ventilation. Our findings concurred with the results of the RECOVERY trial**.** The advantage of our study is that it was conducted on the cohort of patients that presented at our hospital during the initial phase of the COVID-19 pandemic back in March of 2020. At that time, the use of corticosteroids and remdesivir were not established as the standard of care, and hence our study is not confounded by the effects of these medications.

Research perspectives

Given the conflicting results of recent studies on aspirin and COVID-19 illness, it would seem beneficial for future studies to study the effect of chronic daily aspirin use on COVID-19 outcomes. Since our N-126, larger studies with N-1000s may be able to show definitive significance between aspirin and COVID-19. In theory, aspirin is an over the counter, cheap medication with a wide range of properties to battle the ill effects of the virus.

FOOTNOTES

Author contributions: Gogtay M contributed to inception of study idea, data collection, statistical interpretations, and manuscript editing and final submission; Singh Y drafting manuscript, assisting with statistics, proof reading and abstract creation; Bullappa A statistical analysis of data; Scott J inception of study idea, proof reading of manuscript and mentor for the study.

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Country/Territory of origin: United States

ORCID number: Maya Gogtay 0000-0001-9955-7121; Yuvaraj Singh 0000-0003-4970-8870; Asha Bullappa 0000-0002-1567-5241; Jeffrey Scott 0000-0002-1416-508X.

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ORIGINAL ARTICLE

Observational Study

Association of latitude and altitude with adverse outcomes in patients with COVID-19: The VIRUS registry

Aysun Tekin, Shahraz Qamar, Romil Singh, Vikas Bansal, Mayank Sharma, Allison M LeMahieu, Andrew C Hanson, Phillip J Schulte, Marija Bogojevic, Neha Deo, Simon Zec, Diana J Valencia Morales, Katherine A Belden, Smith F Heavner, Margit Kaufman, Sreekanth Cheruku, Valerie C Danesh, Valerie M Banner-Goodspeed, Catherine A St Hill, Amy B Christie, Syed A Khan, Lynn Retford, Karen Boman, Vishakha K Kumar, John C O'Horo, Juan Pablo Domecq, Allan J Walkey, Ognjen Gajic, Rahul Kashyap, Salim Surani, The Society of Critical Care Medicine (SCCM) Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group

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Aysun Tekin, Romil Singh, Mayank Sharma, Diana J Valencia Morales, Rahul Kashyap, Salim Surani, Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905, United States

Shahraz Qamar, Post-baccalaureate Research Education Program, Mayo Clinic College of Medicine and Science, Rochester, MN 55905, United States

Vikas Bansal, Marija Bogojevic, Simon Zec, John C O'Horo, Ognjen Gajic, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905, United States

Allison M LeMahieu, Andrew C Hanson, Phillip J Schulte, Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN 55905, United States

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

Katherine A Belden, Division of Infectious Diseases, Thomas Jefferson University Hospital, Philadelphia, PA 19107, United States

Smith F Heavner, Prisma Health, Greenville, SC 29605, United States

Margit Kaufman, Englewood Health, Englewood, NJ 07631, United States

Sreekanth Cheruku, Divisions of Cardiothoracic Anesthesiology and Critical Care Medicine, Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX 75390, United States

Valerie C Danesh, Center for Applied Health Research, Baylor Scott and White Health, Dallas, TX 75246, United States

Valerie M Banner-Goodspeed, Department of Anesthesiology, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, MA 02215, United States

Catherine A St Hill, Allina Health, Minneapolis, MN 55407, United States

Amy B Christie, Department of Critical Care, Atrium Health Navicent, Macon, GA 31201, United States

Syed A Khan, Division of Critical Care Medicine, Mayo Clinic Health System, Mankato, MN 56001, United States

Lynn Retford, Karen Boman, Vishakha K Kumar, Society of Critical Care Medicine, Mount Prospect, IL 60056, United States

John C O'Horo, Division of Infectious Diseases, Mayo Clinic, Rochester, MN 55905, United States

Juan Pablo Domecq, Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905, United States

Allan J Walkey, Pulmonary Center, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, Evans Center of Implementation and Improvement Sciences, Boston University School of Medicine, Boston, MA 02118, United States

Salim Surani, Department of Pulmonary and Critical Care Medicine, Texas A&M University, Bryan, TX 77807, United States

Corresponding author: Salim Surani, FACP, FCCP, MD, MPH, Doctor, Professor, Department of Pulmonary and Critical Care Medicine, Texas A&M University, 8447 Riverside Pkwy, Bryan, TX 77807, United States. srsurani@hotmail.com

Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) course may be affected by environmental factors. Ecological studies previously suggested a link between climatological factors and COVID-19 fatality rates. However, individual-level impact of these factors has not been thoroughly evaluated yet.

AIM

To study the association of climatological factors related to patient location with unfavorable outcomes in patients.

METHODS

In this observational analysis of the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study: COVID-19 Registry cohort, the latitudes and altitudes of hospitals were examined as a covariate for mortality within 28 d of admission and the length of hospital stay. Adjusting for baseline parameters and admission date, multivariable regression modeling was utilized. Generalized estimating equations were used to fit the models.

RESULTS

Twenty-two thousand one hundred eight patients from over 20 countries were evaluated. The median age was 62 (interquartile range: 49-74) years, and 54% of the included patients were males. The median age increased with increasing latitude as well as the frequency of comorbidities. Contrarily, the percentage of comorbidities was lower in elevated altitudes. Mortality within 28 d of hospital admission was found to be 25%. The median hospital-free days among all included patients was 20 d. Despite the significant linear relationship between mortality and hospital-free days (adjusted odds ratio (aOR) = 1.39 (1.04, 1.86), P = 0.025 for mortality within 28 d of admission; aOR = -1.47 (-2.60, -0.33), P = 0.011 for hospital-free days), suggesting that adverse patient outcomes were more common in locations further away from the Equator; the results were no longer significant when adjusted for baseline differences (aOR = 1.32 (1.00, 1.74), P = 0.051 for 28-day mortality; aOR = -1.07 (-2.13, -0.01), P = 0.050 for hospital-free days). When we looked at the altitude's effect, we discovered that it demonstrated a non-linear association with mortality within 28 d of hospital admission (aOR =

0.96 (0.62, 1.47), 1.04 (0.92, 1.19), 0.49 (0.22, 0.90), and 0.51 (0.27, 0.98), for the altitude points of 75 MASL, 125 MASL, 400 MASL, and 600 MASL, in comparison to the reference altitude of 148 m.a.s.l, respectively. $P = 0.001$). We detected an association between latitude and 28-day mortality as well as hospital-free days in this worldwide study. When the baseline features were taken into account, however, this did not stay significant.

CONCLUSION

Our findings suggest that differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship at the patient level.

Key Words: 28 d mortality; Altitude; COVID-19; Hospital-free days; Latitude; Outcomes

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Core Tip: We detected an association between latitude and mortality within 28 d of admission and hospital-free days in this worldwide study. When the baseline features were taken into account, however, this did not stay significant. Our findings suggest that differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship at the patient level.

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INTRODUCTION

After being identified at the end of 2019, Coronavirus disease 2019 (COVID-19) rapidly disseminated worldwide and affected millions[1,2]. Although studies have shown the efficacy of some medications or the impact of certain conditions on the disease process[3-8], there are still unknown factors that affect the patient outcomes. The investigation of the relationship of disease severity with different environmental settings might provide better insight into the pathogenesis of COVID-19.

A link between climatological factors and Coronavirus Disease 2019 (COVID-19) fatality rates was previously suggested by ecological studies[9-13]. Geographic factors were also demonstrated to impact other respiratory infection processes[14,15]. However, these studies may be subject to the ecological fallacy, in which grouped population-level associations are not observed at the individual level[16]. Large-scale, patient-level cohort studies have thus far not evaluated associations between factors such as altitude and latitude with COVID-19 severity.

The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 registry[17-19] is a global collaboration of partners from 27 countries that provides a novel resource for the investigation of associations between altitude and latitude, with outcomes of individuals with COVID-19, allowing adjustment for baseline factors to evaluate the relationship between COVID-19 disease severity and geographical factors. Using this large cohort, we targeted to assess the relationship of altitude and latitude with unfavorable patient outcomes.

MATERIALS AND METHODS

This study was conducted on the data collected within the scope of the VIRUS: COVID-19 registry. The project was approved as exempt by the institutional review board at Mayo Clinic (IRB:20-002610). Clinical Trials Database registration number for the registry is NCT04323787.

Study population and data collection

All subjects hospitalized with a COVID-19 associated indication (laboratory-confirmed or clinically diagnosed infection) at participating institutions were eligible for inclusion in the VIRUS: COVID-19

registry[20]. The exclusion criteria for the VIRUS Registry study are non-COVID-19 related admissions, Minnesota patients who have not provided research authorization, and readmissions of already included patients. De-identified data were collected through Research Electronic Data Capture software (REDCap, version 8.11.11, Vanderbilt University, Nashville, Tennessee) and stored in a central database hosted by Mayo Clinic[21].

Regarding the analysis for this particular study, all adult subjects admitted between March 15, 2020, and January 15, 2021, were screened for inclusion. Although enrolled in the VIRUS: COVID-19 registry, we excluded pediatric patients (< 18 years old) from this project. Another exclusion criterion was patients enrolled from institutions reporting fewer than 65% of subjects with hospital discharge status. Since those participating centers were unlikely to represent a realistic distribution of outcomes, they were omitted as non-participating. After the application of exclusion criteria, patients of 143 participating hospitals in 21 countries were found to be eligible for inclusion. Detailed inclusion and exclusion criteria for the VIRUS Registry and this project is provided in Supplementary Figure 1.

The patients' residential addresses at the time of diagnosis were not accessible due to the de-identified database. As a surrogate, the location of the participating institutions, which was available for all enrolled patients, was used to determine geographical variables. Latitude and altitude information was retrieved from the Google Earth software[22]. Based on their locations, subjects were grouped according to the elevation above the sea level and the distance from the Equator, regardless of the hemisphere of location[23,24]. Baseline information and disease-related specifics were gathered from the VIRUS Registry.

Outcome of interest

The primary outcome was mortality within 28 d of admission, and the secondary outcome was length of hospital stay. The variable "hospital-free days" (HFD) was used to analyze the impact on hospital length of stay[25], calculated by subtracting the number of admission days from 28; which was 0 for patients who died in the hospital or stayed in the hospital for longer than 28 d. Both outcomes were evaluated independently.

Statistical analyses

The statistical methodology was reviewed by our co-authors from the Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Rochester.

The median and interquartile range (IQR) were used to summarize continuous data. Categorical variables were reported as numbers and percentages. Unadjusted and multivariable-adjusted logistic regression assessed the association with outcomes. To account for the clustering of patients within sites, models were fitted using generalized estimating equations using an exchangeable working correlation for individual hospitals. When the results indicated a non-linear functional structure, they were graphically summarized using the restricted cubic spline fit; otherwise, the linear relationship was defined. Age, gender, race, body mass index, number of days with symptoms prior to admission, symptom groups, the timing of admission with regards to the start of the pandemic, and comorbidities were factored into the models. Unadjusted and multivariable linear regression models assessed the association with HFD using a similar approach. Odds ratios (OR) and 95% confidence intervals for the mortality endpoint were determined per 10-degrees of latitude and 250-meters of altitude in relation to the median reference points, *i.e.*, 39° and 148 meters above sea-level (MASL), respectively. For HFD, the estimate is the expected difference in mean days, similarly displayed per 10 degrees of latitude and 250 meters of altitude.

For missing data among included institutions and patients, multiple imputations assuming data were missing at random using fully conditional specification with 100 imputations was used to impute missing covariates or outcomes. Analyses were performed on each dataset, and results combined to reflect uncertainty due to missingness. Without correcting for multiplicity related to testing the outcomes or testing both altitude and latitude in regression models, statistical significance was specified as $P < 0.05$.

RESULTS

After exclusion of "non-participating sites," 23210 patients with complete data enrolled in the VIRUS registry were evaluated. Among those, 22108 met eligibility criteria after excluding pediatric patients (Supplementary Figure 2, Supplementary Table 1). The median age was 62 (IQR 49-74) years, with 54% males. Among the subjects, 51% of the included were White, 26% were Black, and 65% of the patients were non-Hispanic; 86% had at least one comorbid condition, hypertension (46%) being the most prevalent. When baseline data were analyzed within latitude and altitude groups, patients were more often older on high-latitude locations (locations farther from the Equator). The frequency of patients with comorbidities and the proportion of females also increased with latitude. At higher altitudes, however, females and patients with comorbidities were less prevalent (Table 1).

Table 1 Baseline characteristics and their distribution to latitude and altitudes

Variables	Total (*n* = 22108)	Latitude				Altitude		
		0-15° (*n* = 589)	16-30° (*n* = 1961)	31-45° (*n* = 19163)	46-60° (*n* = 395)	< 500 MASL (*n* = 21122)	500 - 1000 MASL (*n* = 765)	> 1000 MASL (*n* = 221)
Age, median, IQR	62 (49-74)	50 (36-62)	59 (47-70)	62 (49-74)	72 (59-83)	62 (59-74)	58 (46-69)	60 (49-71)
Gender								
Female	9804 (44%)	198 (34%)	797 (41%)	8626 (46%)	183 (46%)	9476 (45%)	255 (33%)	73 (33%)
Male	12025 (54%)	391 (66%)	1163 (59%)	10259 (54%)	212 (54%)	11367 (55%)	510 (67%)	148 (67%)
Race								
White	11210 (51%)	2 (0%)	471 (24%)	10449 (55%)	288 (73%)	10928 (52%)	227 (30%)	55 (25%)
African American	5757 (26%)	74 (13%)	505 (26%)	5145 (27%)	33 (8%)	5738 (27%)	17 (2%)	2 (1%)
Mixed race	785 (4%)	164 (28%)	119 (6%)	501 (3%)	1 (0%)	524 (2%)	129 (17%)	132 (60%)
Asian American	416 (2%)	-	9 (0%)	398 (2%)	9 (2%)	412 (2%)	4 (1%)	0 (0%)
Others	3940 (18%)	349 (59%)	857 (44%)	2670 (14%)	61 (15%)	3122 (15%)	371 (48%)	32 (1%)
Ethnicity								
Hispanic	4592 (21%)	88 (15%)	313 (16%)	4185 (22%)	6 (2%)	4322 (20%)	197 (26%)	73 (33%)
Non-Hispanic	14411 (65%)	354 (60%)	1250 (64%)	12571 (66%)	236 (60%)	14073 (67%)	281 (37%)	57 (26%)
BMI	29.0 (25, 35)	26.7 (24, 28)	28.0 (25, 34)	29.3 (25, 35)	26.7 (23, 32)	29.0 (25, 35)	28.6 (26, 33)	28 (26, 32)
Comorbidities (any)	18991 (86%)	295 (50%)	1580 (81%)	16753 (87%)	363 (92%)	18262 (86%)	578 (76%)	151 (68%)
Hypertension	10267 (46%)	191 (32%)	1050 (54%)	8785 (46%)	241 (61%)	9865 (47%)	322 (42%)	80 (36%)
Diabetes	6473 (29%)	134 (23%)	738 (38%)	5474 (29%)	127 (32%)	6163 (29%)	256 (33%)	54 (24%)
Coronary artery disease	4124 (19%)	29 (5%)	338 (17%)	3678 (19%)	79 (20%)	4017 (19%)	87 (11%)	20 (9%)
Obesity	3794 (17%)	34 (6%)	394 (20%)	3304 (17%)	62 (16%)	3640 (17%)	125 (16%)	29 (13%)
Dyslipidemia	3521 (16%)	7 (1%)	315 (16%)	3168 (17%)	31 (8%)	3422 (16%)	87 (11%)	12 (5%)
Chronic kidney disease	2609 (12%)	5 (1%)	233 (12%)	2295 (12%)	76 (19%)	2543 (12%)	56 (7%)	10 (5%)

BMI: Body mass index; IQR: Interquartile range; MASL: Meters above sea level.

A total of 3451 patients (25% of 13,959 patients with mortality data available) died within 28 d following admission. The median HFD for the general study population was 20 (IQR 3.0-24.0) days. The 28-day mortality rate was higher in higher-latitude locations. Mortality rates were also higher for patients hospitalized in higher altitudes. Additionally, the median HFD was lower for higher latitude and altitude levels (Figure 1).

The unadjusted analysis showed a significant linear association of higher latitude locations associated with increased mortality (OR = 1.39, 95%CI = 1.04, 1.86, P = 0.025) and lower number of HFD (Estimate = -1.47, 95%CI = -2.60, -0.33, P = 0.011) per 10 (degree) latitude. However, after adjustment to the baseline characteristics, there was insufficient evidence to indicate a significant association with both outcomes (adjusted OR (aOR) = 1.32, 95%CI = 1.00, 1.74, P = 0.051 for mortality, and adjusted Estimate = -1.07, 95%CI = -2.13, -0.01, P = 0.050 for HFD) (Table 2).

When evaluating the impact of higher altitudes on adverse outcomes, there was a non-linear association with mortality, which remained significant after adjustment (aOR and 95%CIs for the altitude points of 400 MASL and 600 MASL, compared to the reference altitude of 148 MASL were 0.49 (0.22, 0.90), and 0.51 (0.27,0.98), respectively, P = 0.017) (Table 2). The odds of fatal disease course slightly increased at altitude levels between 125 and 145 MASL; decreased to the lowest around the altitude of 350 MASL, and gradually increased after that point with the increasing altitude (Figure 1C). No association was present with HFD and altitude levels either before or after adjustment.

Table 2 Comparison of outcomes according to latitude and altitudes

Study outcomes	Latitude						Altitude					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
	Estimate	95%CI	*P* value	Estimate	95%CI	*P* value	Estimate	95%CI	*P* value	Estimate	95%CI	*P* value
28 d mortality	1.39	(1.04, 1.86)	0.025	1.32	(1.00, 1.74)	0.051	RCS, *P* value non-linearity ≤ 0.001, *P* value overall association = 0.001			RCS, *P* value non-linearity = 0.049, *P* value overall association = 0.017		
Hospital-free days	-1.47	(-2.60, -0.33)	0.011	-1.07	(-2.13, -0.01)	0.050	0.14	(-0.37, 0.64)	0.587	0.10	(0.37, 0.56)	0.683

For the altitude points of 75 MASL, 125 MASL, 400 MASL, and 600 MASL, compared to the reference altitude of 148 MASL; the adjusted odds ratios and 95%CIs regarding 28 d mortality were 0.96 (0.62,1.47), 1.04 (0.92,1.19), 0.49 (0.22, 0.90), and 0.51 (0.27, 0.98), respectively. CI: Confidence interval; ICU: Intensive care unit; MASL: Meters above sea level; RCS: Restricted cubic spline.

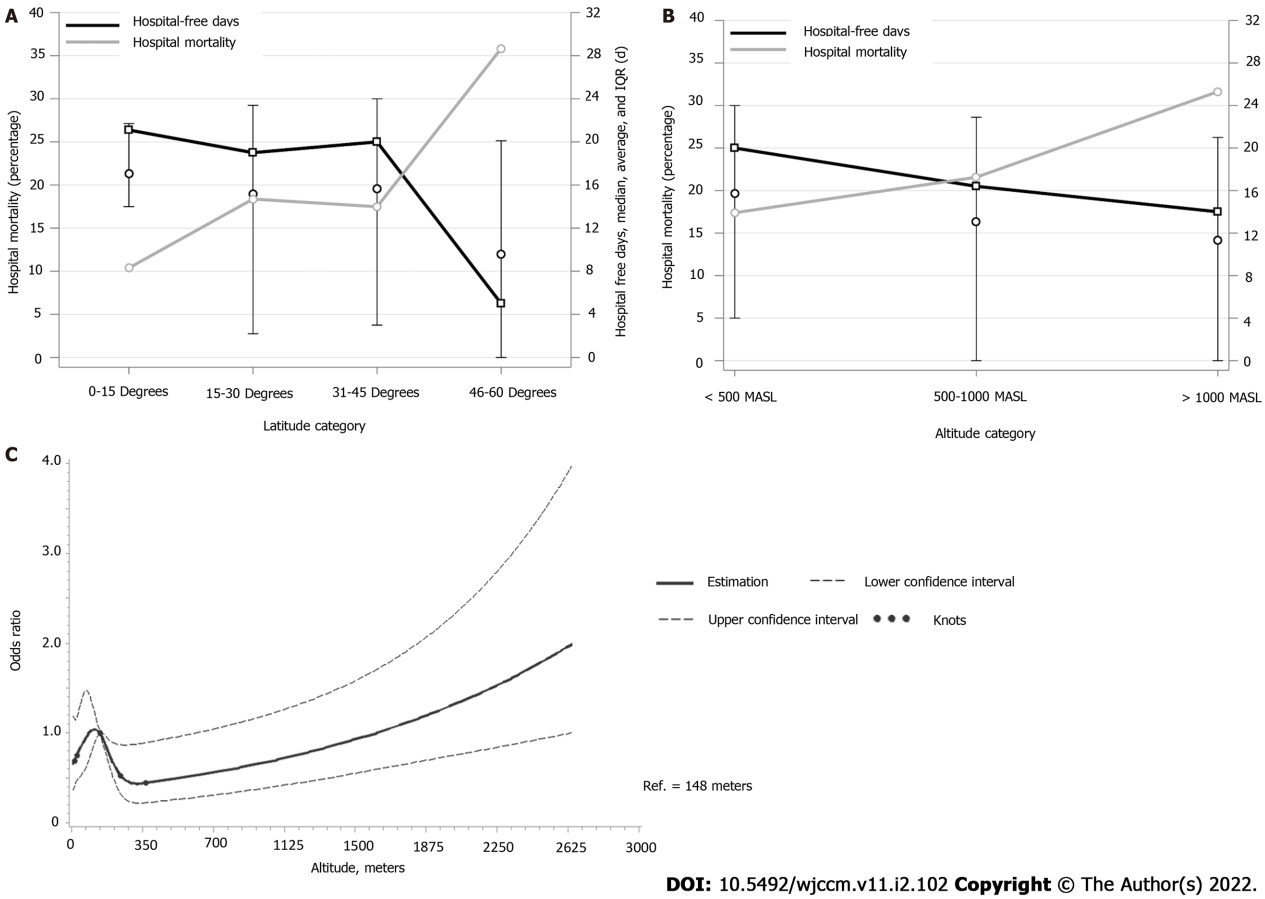

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Figure 1 Distribution of outcomes and adjusted associations to different altitude and latitude levels. A: Outcomes and latitude; B: Outcomes and altitude; C: Adjusted associations between 28 d mortality with altitude, shown using restricted cubic spline with 5 knots. IQR: Interquartile range; MASL: Meters above sea level.

DISCUSSION

We reported the distribution of patient outcomes to different altitudes and latitudes within an international COVID-19 registry. In our study, even though 28-day mortality increased and the number of HFD decreased in high-latitude locations on unadjusted estimates, the associations were not significant after adjustment for patients' characteristics. In the adjusted model, the odds of mortality were associated with altitude, gradually increasing after 350 MASL.

Older age and certain comorbidities were shown to be associated with unfavorable disease outcomes for COVID-19 patients[26,27]. Populations living in higher latitudes were shown to have a higher median age and more frequent comorbid conditions[28]. Furthermore, individuals living at higher elevations from the sea level were shown to have less comorbidity burdens[12]. Our study sample also noted a similar distribution of median age and comorbidities to different latitude and altitude levels.

Prior studies suggested that the variation of mortality rates in different latitude settings was partly attributable to baseline characteristics of populations[32,33]. However, others detected a relationship between humidity or sunlight exposure and case rates, which was thought to be related to viral dynamics[11,34]. In this study, the association of mortality within 28 d of admission and HFD with latitude, although statistically significant in the unadjusted analysis, was not statistically significant after case-mix adjustment. Our findings indicate that differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship with environmental factors at the individual level[16].

Studies evaluating the impact of altitude on case and fatality rates of COVID-19 illustrated that higher altitude had a protective effect, possibly due to physiological and habitual characteristics of the individuals and environmental factors impacting virus survival[12,35]. Conversely, in our study, mortality gradually increased with increasing altitude after 350 MASL, suggesting the impact of environmental hypoxia resulting in the fragility of pulmonary functions or coagulation disorders. Although our results might suggest an impact of different elevation levels on disease outcomes, not having enough variation in altitude to test the impact of atmospheric oxygen pressure impedes our ability to conclude the actual effect of higher altitudes. Thus, our analysis results should be interpreted with caution.

Studies that evaluated the effects of latitude and altitude in patients with COVID-19 were epidemiological investigations that were conducted on populations rather than on individual patients. Thus, they are subject to the bias of aggregated variables rather than providing insight for a causal relationship[16]. This is the first study to evade ecological fallacy by considering individual baseline characteristics to the best of our knowledge. Thus, it might provide a better insight into the causal effect of environmental factors on adverse outcomes.

The most important limitation was the small sample variety in lower latitude and higher altitude environments. Especially not having patients from a wide range of altitude levels precluded drawing definitive conclusions about the impact of higher altitudes. Another limitation is being conducted exclusively on hospitalized patients, which might subject our results to collider bias[36]. Although our outcomes of interest might have ameliorated this limitation's impact, it still hampers the generalizability of our results. Additionally, variations in patient management among different regions might have an impact on our results. Another weakness of our analysis is the lack of information about patients' home location (exempt IRB only allowed de-identified data use) and institutions' geographical locations as a surrogate. However, travel restrictions imposed during the study period might have kept patients confined to their primary residence and resultant nearby hospital admissions. Furthermore, although it was suggested as a contributor to disease severity, especially in higher latitudes, vitamin D levels were not incorporated in the analysis due to the unavailability. However, the timing of the study encompassing enough sunlight hours for the Northern Hemisphere might mitigate this limitation's impact. Also, the number of patients included from the countries outside of the United States was limited. Moreover, to increase the accuracy of the frequency measurement, several institutions were not included in the study due to incomplete data variables.

CONCLUSION

Although 28 d mortality and HFD seemed to be associated with latitude, the association did not remain significant after adjustment. Our results might indicate that reported variations in COVID-19 in different environmental conditions might be based on individual patient characteristics rather than geographic factors.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) has taken the world by storm. Several factors were attributed to the spread of the virus including altitude and latitude. We studied the relationship of location with unfavorable patient outcomes in COVID-19.

Research motivation

There were variations in the case and fatality rates in different regions of the world. Using a large cohort, we aimed to assess if latitude or altitude had an impact on the disease course of the COVID-19

on the individual patient level.

Research objectives

To study the association of certain aspects of location with unfavorable outcomes in COVID-19.

Research methods

An observational study using the Virus COVID-19 Registry was used to analyze for mortality within 28 d of admission and hospital length of stay. Adjusting for baseline parameters and admission date, multivariable regression modeling was utilized.

Research results

Twenty-two thousand one hundred eight patients from 21 countries were included. Mortality within 28 d of hospital admission was found to be 25%. The median number of hospital-free days among all included patients was 20 days. Despite the linear association between mortality within 28 d of hospital admission and hospital-free days and increasing latitude being significant, indicating that adverse disease outcomes were more frequent in locations further away from the Equator, the association was not significant after adjusting for baseline characteristics. A non-linear association between altitude and 28-day mortality was seen.

Research conclusions

There seemed to be an association of latitude with mortality within 28 d of admission and hospital-free days, which was nonsignificant when adjusted for baseline characteristics.

Research perspectives

The differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship with environmental factors at the individual level.

FOOTNOTES

Author contributions: Tekin A and Kashyap R prepared the first draft of this manuscript; Qamar S, Singh R, Bansal V, Sharma M, Bogojevic M, and Deo N contributed to the design of the study and the data collection; LeMahieu AM, Hanson AC, and Schulte PJ conducted the analysis of the data; Zec S, Valencia Morales DJ, Belden KA, Heavner SF, Kaufman M, Cheruku S, Danesh VC, Banner Goodspeed VM, St. Hill CA, Christie AB, and Khan SA contributed to data collection; Retford L and Boman K helped with the data retrieval; Kumar VK, O'Horo JC, Domecq JP, Walkey AJ, Gajic O, and Surani S reviewed, edited, and provided critical feedback on the manuscript.

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Country/Territory of origin: United States

ORCID number: Aysun Tekin 0000-0002-1891-2118; Shahraz Qamar 0000-0002-9097-0443; Romil Singh 0000-0003-3777-5670; Vikas Bansal 0000-0001-6047-5559; Mayank Sharma 0000-0001-7808-9912; Allison LeMahieu 0000-0003-1554-795X; Andrew C Hanson 0000-0003-4673-5486; Phillip J Schulte 0000-0001-6575-4741; Marija Bogojevic 0000-0001-5460-3753; Neha Deo 0000-0002-0583-8916; Simon Zec 0000-0002-4353-8535; Diana J Valencia Morales 0000-0001-8835-9541; Katherine A Belden 0000-0002-2556-3083; Smith F Heavner 0000-0003-0912-0407; Margit Kaufman 0000-0003-4535-6214; Sreekanth Cheruku 0000-0003-3185-0000; Valerie C Danesh 0000-0002-2078-2578; Valerie M Banner-Goodspeed 0000-0002-7644-2521; Catherine A St Hill 0000-0002-6113-5705; Amy B Christie 0000-0001-9100-7045; Syed A Khan 0000-0002-2452-2079; Lynn Retford 0000-0002-1618-7063; Karen Boman 0000-0001-6864-2569; Vishakha K Kumar 0000-0003-4998-5114; John C O'Horo 0000-0002-0880-4498; Juan Pablo Domecq 0000-0002-8540-9862; Allan J Walkey 0000-0003-4685-6894; Ognjen Gajic 0000-0003-4218-0890; Rahul Kashyap 0000-0002-4383-3411; Salim Surani 0000-0001-7105-4266; The Society of Critical Care Medicine (SCCM) Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group 0000-0000-0000-0000.

Corresponding Author's Membership in Professional Societies: Society of Critical Care Medicine; American College of Chest Physicians.

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LETTER TO THE EDITOR

Potential role of vitamin D in patients with diabetes, dyslipidaemia, and COVID-19

Ming-Ke Wang, Xue-Lu Yu, Li-Yun Zhou, Hong-Mei Si, Ju-Fen Hui, Ji-Shun Yang

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Ming-Ke Wang, Xue-Lu Yu, Li-Yun Zhou, Hong-Mei Si, Ju-Fen Hui, Department of Disease Control and Prevention, Naval Medical Center of PLA, Naval Medical University, Shanghai 200052, China

Ji-Shun Yang, Medical Care Center, Naval Medical Center of PLA, Naval Medical University, Shanghai 200052, China

Corresponding author: Ji-Shun Yang, MD, PhD, Director, Medical Care Center, Naval Medical Center of PLA, Naval Medical University, No. 338 Huaihai West Road, Shanghai 200052, China. jasunyang@foxmail.com

Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 has become a worldwide public health crisis. Studies have demonstrated that diabetes and dyslipidaemia are common comorbidities and could be high-risk factors for severe COVID-19. Vitamin D, a group of fat-soluble compounds responsible for intestinal absorption of calcium, magnesium, and phosphate, has been widely used as a dietary supplement for the prevention and treatment of numerous diseases, including infectious and non-infectious diseases, due to its high cost-effectiveness; safety; tolerability; and anti-thrombotic, anti-inflammatory, antiviral, and immunomodulatory properties. In this letter to the editor, we mainly discuss the potential role of vitamin D in patients with diabetes, dyslipidaemia, and COVID-19.

Key Words: Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus-2; Vitamin D; Diabetes; Dyslipidaemia

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Core Tip: Diabetes and dyslipidaemia are common comorbidities in patients with coronavirus disease 2019 (COVID-19), and these comorbidities are often associated with worse clinical outcome. In this letter to the editor, we hypothesize that vitamin D may be a prognostic factor and could be a promising preventive measure and treatment for patients with diabetes, dyslipidaemia, and COVID-19.

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TO THE EDITOR

We read with great interest the recent article by Iglesias *et al*[1] entitled "Retrospective analysis of anti-inflammatory therapies during the first wave of coronavirus disease 2019 (COVID-19) at a community hospital", which demonstrated the survival benefit associated with anti-inflammatory therapy with glucocorticoids and revealed that combination treatment with tocilizumab and glucocorticoids could provide the most benefit in critically ill patients with COVID-19 caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). However, monotherapy with tocilizumab as an interleukin 6 (IL-6) antagonist was not associated with an increase in survival among critically ill patients with COVID-19, which could be explained by the fact that tocilizumab non-selectively blocks both anti-inflammatory and pro-inflammatory actions of IL-6[2]. Meanwhile, vitamin D, a group of fat-soluble compounds, may have advantages over tocilizumab as an IL-6 immunomodulator by potentially reducing the pro-inflammatory effects, but avoiding the deleterious effects on the anti-inflammatory actions of IL-6 in patients with COVID-19[2]. Additionally, vitamin D could modulate the innate and adaptive immune responses, and its deficiency is associated with increased morbidity and mortality in SARS-CoV-2 infection[3]. Vitamin D status may be a potential predictor of COVID-19 outcomes, and vitamin D supplementation could be a promising therapeutic and preventive method against COVID-19, due to its high cost-effectiveness; safety; tolerability; and anti-thrombotic, anti-inflammatory, antiviral, and immunomodulatory properties[3,4].

Another published article in your journal by Gkoufa *et al*[5] entitled "Elderly adults with COVID-19 admitted to intensive care unit: A narrative review" found that diabetes and hypercholesterolemia were common comorbidities in older patients with COVID-19 and these comorbidities were often associated with worse clinical outcome. Previous studies also showed that vitamin D deficiency was associated with diabetes and dyslipidaemia[6,7]. Unfortunately, about 30%-50% of people in the world have vitamin D deficiency or insufficiency, and vitamin D deficiency has been a global health problem[8]. Singh *et al*[3] reviewed the evidence of vitamin D deficiency in patients with diabetes and COVID-19, and they proposed that diabetes increased the tendency for infection and COVID-19, vitamin D deficiency was linked to both diabetes and an increased risk of infections, including COVID-19, and vitamin D supplementation may be a safe, cheap, and simple adjuvant therapy in patients with diabetes and COVID-19. Verdoia *et al*[4] reviewed the mechanisms of action of vitamin D and its potential interaction with SARS-CoV-2 infection, and they reported that vitamin D plays an important protective role in the cardiovascular system, immune system, respiratory system, and glucose-lipid metabolism. Therefore, we hypothesize that vitamin D status has prognostic significance in diabetes and dyslipidaemia, and vitamin D supplementation could exert a triple preventive and therapeutic effect in patients with diabetes, dyslipidaemia, and COVID-19.

In summary, diabetes and dyslipidaemia are common comorbidities in patients with COVID-19. Patients with diabetes and dyslipidaemia are more prone to SARS-CoV-2 infection, and they have poor clinical outcomes. Vitamin D may be a potential prognostic factor and could be a promising preventive measure and treatment for patients with diabetes, dyslipidaemia, and COVID-19. Notably, hypervitaminosis D is a rare but potentially serious condition, and it should be avoided when recommending fat-soluble vitamin D supplementation in the era of COVID-19[9]. Certainly, more robust studies are still required to ascertain the prognostic significance and one-arrow three-vulture effect of vitamin D in patients with diabetes, dyslipidaemia, and COVID-19.

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Country/Territory of origin: China

ORCID number: Ming-Ke Wang 0000-0001-9918-0491; Xue-Lu Yu 0000-0002-8527-2093; Li-Yun Zhou 0000-0003-1413-8679; Hong-Mei Si 0000-0003-1175-6594; Ju-Fen Hui 0000-0001-7816-0635; Ji-Shun Yang 0000-0001-7160-706X.

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