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MINIREVIEWS

SARS-CoV-2 viral load in the upper respiratory tract and disease severity in COVID-19 patients

Wattana Leowattana, Tawithep Leowattana, Pathomthep Leowattana

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Abstract

Due to the disease's broad clinical spectrum, it is currently unclear how to predict the future prognosis of patients at the time of diagnosis of coronavirus disease 2019 (COVID-19). Real-time reverse transcription-polymerase chain reaction (RT-PCR) is the gold standard molecular technique for diagnosing COVID-19. The number of amplification cycles necessary for the target genes to surpass a threshold level is represented by the RT-PCR cycle threshold (Ct) values. Ct values were thought to be an adequate proxy for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load. A body of evidence suggests that SARS-CoV-2 viral load is a possible predictor of COVID-19 severity. The link between SARS-CoV-2 viral load and the likelihood of severe disease development in COVID-19 patients is not clearly elucidated. In this review, we describe the scientific data as well as the important findings from many clinical studies globally, emphasizing how viral load may be related to disease severity in COVID-19 patients. Most of the evidence points to the association of SARS-CoV-2 viral load and disease severity in these patients, and early anti-viral treatment will reduce the severe clinical outcomes.

Key Words: Severe acute respiratory syndrome coronavirus-2; Viral load; Upper respiratory tract; Coronavirus disease 2019 patients; Disease severity; Clinical outcome

Core Tip: Real-time reverse transcription-polymerase chain reaction is regarded as the gold standard confirmatory test for coronavirus disease 2019 (COVID-19). Cycle threshold (Ct) values can be used to diagnose or forecast severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection since they are associated with virus load. Numerous differences exist in several clinical trials with small or large sample sizes, indicating a substantial positive correlation between the Ct value and disease severity in COVID-19. In this context, a literature review was conducted to address information gaps about the relationship between Ct levels and disease severity in COVID-19 patients globally. The majority of the data indicated a link between SARS-CoV-2 viral load and disease severity in these patients, and early anti-viral therapy will minimize the severity of the clinical outcomes.

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INTRODUCTION

Prior to November 2019, six coronaviruses (CoVs) were known to infect humans and cause respiratory disease: OC43, 229E, HKU1, and NL63, four community-acquired CoVs that are endemic in humans, as well as severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV), two highly pathogenic CoVs that have zoonotic transmission followed by variable transmission between humans[1-5]. A new CoV discovered in late 2019 in Wuhan, Hubei Province, China has recently spread worldwide, causing a serious pandemic. SARS-CoV-2 was the name given to the new CoV, and the condition was dubbed coronavirus disease 2019 (COVID-19). SARS-CoV-2 spread rapidly from person to person, resulting in a pandemic that affected every province in China and eventually more than 203 nations and territories around the globe[6-7]. As of March 22, 2022, the World Health Organization has received reports of nearly 459 million cases of COVID-19, including more than 6 million deaths[8].

Viral load is used to diagnose severe viral infections of the respiratory system, as well as to track disease progression and treatment. By evaluating the value of the cycle threshold (Ct) of reverse transcription-polymerase chain reaction (RT-PCR), the SARS-CoV-2 viral load may be determined from the patient's viral RNA at a certain concentration. The lower the Ct values, the greater the viral load[9]. In contrast to other viral infections, no pathogen-specific prognostic indicators for SARS-CoV-2 are readily accessible. The first prognostic evaluation of individuals infected with SARS-CoV-2 may benefit from viral biomarkers capable of forecasting COVID-19 development in addition to the existing risk factors for severity. It is presently disputed whether the SARS-CoV-2 viral load affects the severity and course of the disease in this regard[10-13]. According to recent research, there may be a correlation between viral load and the severity of SARS-CoV-2 pneumonia, the degree of hypoxemia, the risk of mortality, as well as hematological, biochemical, and inflammatory alterations. However, diverse recruiting criteria have made it difficult to obtain a final, definite conclusion on the association between early nasopharyngeal viral load and individual outcomes[14-16]. The goal of this review is to ascertain if the SARS-CoV-2 Ct at diagnosis could anticipate the severity of COVID-19 and the outcomes of these patients.

SARS-COV-2 VIRAL LOAD IS ASSOCIATED WITH DISEASE SEVERITY

Knudtzen *et al*[17] conducted a prospective cohort study of adult COVID-19 patients with PCR-positive SARS-CoV-2 airway samples to determine the association between cycle quantification (Cq)-values, hospitalization, and disease severity in 87 outpatients and 82 inpatients. The findings revealed that 31 of the 82 hospitalized patients (38.0%) had severe COVID-19 disease and had considerably lower baseline Cq-values than patients with moderate disease severity (median Cq-values = 24.8 *vs* 28.1, P = 0.01). They also discovered a statistically significant link between lower Cq-values and a higher risk of severe disease outcome (odds ratio [OR] = 0.89, 95% confidence interval (CI): 0.81-0.98, P = 0.018), which was independent of the timing of the test in relation to symptom onset and the presence of confounding factors such as airway sample type. When the date of the test and confounding variables were controlled for, they observed no relationship between lower baseline Cq-values in outpatients infected with SARS-CoV-2 and a greater likelihood of hospitalization. They concluded that SARS-CoV-2 PCR Cq-values were correlated with the time since symptoms began. Early in the clinical course, Cq-values were low as a sign of high viral loads, but Cq-values were not shown to be a predictor of hospitalization. On the other hand, lower Cq-values were found to be indicative of more disease severity in hospitalized patients.

Kawasuji *et al*[18] performed a retrospective cohort study to investigate the concentrations of SARS-CoV-2 RNA in the blood (RNAemia) and in the nasopharyngeal cavity, as well as their relationship with clinical severity in 56 COVID-19 patients. On admission, 19.6% (11/56) of patients had RNAemia, followed by 1.0% (1/25), 50.0% (6/12), and 100.0% (4/4) of intermediate, severe, and critically ill patients, respectively. Patients with RNAemia required more frequent oxygen supplementation (90.0% *vs* 13.3%), intensive care unit (ICU) admission (81.8% *vs* 6.7%), and invasive mechanical ventilation (27.3% *vs* 0.0%). The median viral load of nasopharyngeal swabs in patients with RNAemia was significantly higher in critically ill patients (5.4 Log_{10} copies/μL) than in moderate-severe cases (2.6 Log_{10} copies/μL), and significantly higher in non-survivors (6.2 Log_{10} copies/μL) than in survivors (3.9 Log_{10} copies/μL). They discovered a significant percentage of patients with SARS-CoV-2 RNAemia and a relationship between RNAemia and disease severity. Furthermore, among RNAemia patients, the viral loads of nasopharyngeal swabs were correlated with disease severity and death, suggesting the possibility of combining serum testing with nasopharyngeal tests as a prognostic indicator for COVID-19, with better quality than each test.

The connection between nasopharyngeal viral loads, host variables, and illness severity in 1122 SARS-CoV-2-infected patients was examined by Maltezou *et al*[19]. There were 309 (27.5%) patients with a high viral load, 316 (28.2%) with a moderate viral load, and 497 (44.3%) with a low viral load. In univariate analysis, individuals with high viral loads were older, had more comorbid diseases, required intubation for symptomatic disorders, and eventually passed away. Patients with a high viral load spent more time in the critical care unit and required more intubation than patients with a low viral load. Furthermore, individuals with chronic cardiovascular disease, hypertension, chronic lung disease, immunosuppression, obesity, and chronic neurological disease were more likely to have high viral loads. They concluded that viral load in the nasopharynx may be used to identify patients at high risk of morbidity or poor outcome.

Zheng *et al*[20] conducted a retrospective cohort study on 96 consecutively hospitalized COVID-19 patients, including 22 with moderate disease and 74 with severe disease, to assess viral loads at various phases of disease progression. After admission, 3497 respiratory, stool, serum, and urine samples were obtained from patients and tested for SARS-CoV-2 RNA viral load. RNA was also found in the feces of 55 (59%) of the patients and the serum of 39 (41%) of the patients. One patient's urine sample tested positive for SARS-CoV-2. The median duration of the virus in feces (22 d) was substantially longer than that in respiratory (18 d) and serum samples (16 d). Furthermore, the median duration of the virus in patients with severe disease (21 d) was substantially longer than that in patients with moderate disease (14 d). In the moderate group, viral loads peaked in respiratory samples in the second week after the illness started, but in the severe group, viral loads remained high throughout the third week. Virus duration was greater in individuals over the age of 60 and in men. They proposed that the duration of SARS-CoV-2 RNA in stool samples is significantly longer than that in respiratory and serum samples, emphasizing the importance of improving stool sample management in epidemic prevention and control and that the virus persists longer with higher load and peaks later in the respiratory tissue of patients with severe disease.

Aydin *et al*[21] investigated the predictive significance of viral load identified in the saliva of 300 COVID-19 patients in the early stages of illness. The results showed a mean Ct-value of 25.30 in the mild illness group, 19.85 in the intermediate disease group, 16.75 in the severe disease group, and 15.48 in the critical disease group. The pattern of the mean Ct-value of the oro-nasopharyngeal swab was similar to that of saliva. The authors concluded that the Ct-value of saliva and oro-nasopharyngeal swab might be used to predict disease severity.

de la Calle *et al*[14] performed a retrospective study of 455 hospitalized patients with a confirmed diagnosis of SARS-CoV-2 infection using prospective computerized medical data. The study population was separated into three groups based on the Ct value obtained upon admission: Patients with high viral load (Ct < 25), those with intermediate viral load (Ct 25-30), and those with low viral load (Ct > 30). The researchers discovered that 130 (28.6%) patients had a high viral load, 175 (38.5%) had an intermediate viral load, and 150 (33%) had a low viral load. They discovered that 120 (26.4%) patients died while they were in the hospital, and that 161 (35.4%) patients experienced respiratory failure after spending a median of 9 d there. High viral loads were associated with increased respiratory failure and a higher mortality rate at 30 d following admission in these patients. However, the risk of ICU admission was greater among patients with low and intermediate viral loads (12.3% *vs* 6.2%, $P = 0.054$). Septic shock, acute renal damage, venous thrombosis, hepatitis, or major adverse cardiovascular events were not different across groups. According to the authors, a useful prognostic indicator for the beginning of respiratory failure is the Ct value of RT-PCR in nasopharyngeal swabs at the time of admission.

Kwon *et al*[22] conducted a study on 31 hospitalized COVID-19 patients to investigate viral load, antibody responses to SARS-CoV-2, and cytokines/chemokines along the illness course, as well as to find parameters linked to disease severity. Asymptomatic and moderate patients had lower viral loads and longer viral shed than severe and critical cases. Unlike plasma IgG, which grew gradually and remained stable during hospitalization, plasma IgM peaked 3 wk after symptoms started and then declined. The antibody response was somewhat delayed but greater in severe and critical cases than in others. High levels of interferon (IFN)-α, IFN-γ induced protein-10, chemokine generated by IFN-γ, and interleukin-6 were linked with the severity of COVID-19 5-10 d after symptom onset. The authors hypothesized that a high viral load in the respiratory tract, as well as excessive cytokine and chemokine production between 1 and 2 wk after the onset of symptoms, was substantially linked with the severity of COVID-19.

Piubelli *et al*[23] conducted a retrospective analysis to assess the viral load of 373 confirmed COVID-19 patients seen in the emergency department between March 1, 2020 and May 31, 2020. According to the authors, 281 COVID-19 individuals were identified in March, 86 in April, and 6 in May. Along with a decline in the number of cases, they observed a considerable fall in the proportion of patients requiring critical care, which fell from 6.7% (19/281) in March to 1.1% (1/86) in April, and to none in May. In terms of viral load, they noticed a tendency for Ct to rise from a median of 24 to 34 between March and May, particularly in non-ICU patients. They concluded that throughout the pandemic, they saw a dramatic decline in severe COVID-19 patients that required critical care in addition to the declining viral load.

Shlomai *et al*[13] studied 170 hospitalized COVID-19 patients to see if there was a link between viral load at the time of admission, lung inflammation, and disease prognosis. The authors discovered that non-survivors and mechanically ventilated patients (n = 21) had a considerably greater virus load (8-fold, Ct = 23.43, P = 0.0001) than surviving non-intubated patients (n = 149, Ct = 29.55, P = 0.0001). Furthermore, a multivariate study adjusted for age, gender, and blood oxygen saturation $(BOS)_{min}$ found that low viral load was linked with a lower risk of mechanical ventilation and death (OR = 0.90, 95%CI: 0.81-0.99, P = 0.046). Furthermore, both BOS and patient age were independently related to mechanical ventilation and mortality (OR = 0.91, 95%CI: 0.84-0.98, P = 0.009 for BOS and OR = 1.05, 95%CI: 1.004-1.097 for patient age). They concluded that their data indicated a strong link between nasopharyngeal viral load and hypoxemia, as well as worse clinical outcomes in COVID-19 patients hospitalized.

In a study of 448 COVID-19 patients, Soria *et al*[24] looked at the relationship between viral load, as measured using nasopharyngeal swabs, and the severity of the illness. They clinically categorized individuals as having mild, moderate, or severe COVID-19 based on a variety of clinical characteristics such as the need for hospitalization, the necessity for oxygen treatment, admission to critical care units, and/or mortality. The authors discovered a statistically significant relationship between viral load and disease severity, with higher viral load associated with a worse clinical prognosis, independent of several previously identified risk factors such as age, gender, hypertension, cardiovascular diseases, diabetes, obesity, and pulmonary diseases.

Trunfio *et al*[25] conducted a study on 200 confirmed COVID-19 patients to see if the SARS-CoV-2 Ct value at diagnosis might predict COVID-19 disease severity, clinical symptoms, and 6-mo sequelae. Patients were divided into three groups based on diagnostic Ct values discovered from the initial swab: Ct 20, Group A; Ct = 20 - 28, Group B; and Ct > 28, Group C. The severity of the disease was graded on a six-point scale: Death, hospitalization with intubation, hospitalization needing continuous positive airway pressure support, hospitalization requiring low-flow wall oxygen to reservoir mask assistance, hospitalization without oxygen support, and no hospitalization. There were 168 survivors and 32 deaths among the 200 individuals. The range for the median age was 43-69. There were 116 (58.0%) men, and 188 of them were of European descent (94.0%). Patients with SARS-CoV-2 Ct were distributed as follows: 55 in Group A (27.5%), 55 in Group B (27.5%), and 90 in Group C (45.0%). Even after controlling for the time from COVID-19 onset to swab collection, the linear Ct values were negatively associated with the number of comorbidities per patient. Hospitalization-related patients were seen in Group A more frequently than in Group C (74.5% *vs* 56.7%). The severity of COVID-19 was substantially higher in Group A than in Groups B and C. With respect to Ct, there was an inverse distribution in the five categories of illness severity. Finally, 6-mo results for COVID-19 were worse in Group A than in the other groups; only 29.1% of patients in Group A had fully recovered at this point, compared to 70.9% and 80.0% in Groups B and C, respectively. Furthermore, Group A had a greater fatality rate (36.4%) than the other groups (Group B had a 12.7% lethality rate and Group C had a 5.6% lethality rate). After controlling for confounding variables, in multivariate analysis, lower SARS-CoV-2 Ct levels were independently associated with a greater risk of COVID-19-related death, along with older age and more comorbidities. The authors showed a correlation between COVID-19-related deaths, disease severity, the number of signs and symptoms at diagnosis, and the persistence of sequelae at 6 mo in symptomatic hospitalized and non-hospitalized patients, and the Ct value detected in nasopharyngeal swabs collected within the first week of COVID-19 onset.

Tsukagoshi *et al*[26] conducted a study on 286 confirmed COVID-19 patients to assess the links between epidemiological data, viral load, and disease severity (15 fatal cases, 133 symptomatic cases, and 138 asymptomatic cases). Compared to the number of viral copies at the time of sample collection, fatal cases had $3.57 \pm 4.70 \times 10^9$ copies/mL, symptomatic cases had $3.92 \pm 1.60 \times 10^8$ copies/mL, and asymptomatic cases had $4.92 \pm 1.48 \times 10^7$ copies/mL. These findings imply that the viral loads of fatal and symptomatic patients were greater than those of asymptomatic cases. According to the authors, a high viral load of SARS-CoV-2 in elderly patients at an early stage of the disease, particularly those with pneumonia symptoms, results in a bad prognosis. Therefore, in such circumstances, we should intervene early to avoid the condition's progressing to a severe degree.

Wang *et al*[27] conducted a study on 12 seriously ill and 11 slightly ill COVID-19 patients to explore the immune response and its link with clinical outcomes. The rates of viral replication, neutralizing antibody responses, and cross-reactivity with other human respiratory CoVs were also examined for use in the diagnosis, prognosis, and epidemiological studies. All 23 patients provided 461 clinical samples (84 nasal swabs, 59 throat swabs, 36 sputum samples, 90 fecal samples, 79 urine tests, and 113 plasma samples), including 1 stomach biopsy. They discovered that the majority of patients with severe illness shed viral loads for up to 30-40 d after beginning, but the majority of slightly unwell individuals had no detectable viral loads 15 d after onset. The peak viral load differed significantly between severe and moderate patients. The viral loads in the respiratory samples were larger in the severe group than in the mild group, and they gradually decreased with time. The SARS-CoV-2 was mostly found in respiratory samples. However, in the majority of critically ill patients, feces remained positive for viral RNA for an extended period of time. IgM responses in patients with severe disease increased within 1 to 2 wk after beginning and were progressively reduced after 4 wk, but IgM responses in patients with moderate disease were substantially lower. The majority of the mildly unwell patients (8/11) did not develop substantial IgM antibodies throughout the disease course, demonstrating that the IgM diagnosis was not sensitive for mildly ill individuals. IgG responses appeared 10-15 d after the initiation. The majority of patients had high levels of IgG antibodies that lasted at least 6 wk.

Faíco-Filho *et al*[28] conducted a retrospective cohort analysis on 875 confirmed COVID-19 patients to assess the relationship between SARS-CoV viral load and mortality. Fifty percent (439/875) of these patients had mild disease, 30.4% (266/875) had moderate disease, and 19.5% (170/875) had severe disease. In these COVID-19 individuals, a Ct value of 25 indicated a high viral load, which was independently related to death. They concluded that the SARS-CoV-2 virus load at admission was independently linked with death among hospitalized COVID-19 patients.

Pérez-García *et al*[29] conducted a retrospective study of 255 SARS-CoV-2–infected patients to determine the viral RNA content and expression of selected immune genes in the upper respiratory tract (nasopharynx), as well as their correlation with severe COVID-19. In the beginning, patients were split into three groups based on severity: 85 outpatients who underwent emergency room examinations and were discharged within the first 24 h (mild cases), 87 inpatients in medicine wards who did not require critical care (moderate cases), and 83 critical patients who were admitted to the ICU, or who passed away within 28 d of hospital admission (severe cases), and 30 healthy individuals were used as the control group. Interferon-stimulated gene 15 (ISG15), interferon-β (IFN-β), interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), retinoic acid-inducible gene I (RIGI), tumor necrosis factor (TNF-β), interleukin 6 (IL-6), and chemokine (C-C motif) ligand 5 (CCL5) were all expressed at higher levels in COVID-19 patients. Individuals with severe COVID-19 had considerably greater SARS-CoV-2 viral load, IFN-β, IFIT1, IL-6, and IL-8 levels than patients with mild or moderate illness, although CCL5 values were significantly lower. They also found that ISG15, RIGI, TNF-β, IL-6, and CXCL10 strongly correlated with SARS-CoV-2 virus load. In adjusted regression models, SARS-CoV-2 viral load was a risk factor, but CCL5 was a protective factor for ICU admission or mortality during hospitalization. They also discovered significant relationships between the SARS-CoV-2 viral load and CCL5 in both cohorts when the entire cohort was divided in half, demonstrating a strong correlation between the severity of COVID-19 and both high levels of SARS-CoV-2 virus load and low levels of CCL5 expression. They concluded that a number of innate immune genes are stimulated by SARS-CoV-2 replication in the nasopharyngeal mucosa. Low CCL5 expression levels and high SARS-CoV-2 viral loads were associated with ICU admission or fatality, despite the fact that CCL5 was the best predictor of COVID-19 severity.

Guo *et al*[30] studied the relationship between SARS-CoV-2 viral load and disease severity in 195 hospitalized COVID-19 patients. The differences in clinical characteristics across four groups (mild, moderate, severe, and critical) and two groups (severe *vs* non-severe) were analyzed using one-way ANOVA and the student's *t*-test, respectively. More severe patients appear to have the following characteristics: Older age, underlying diseases, higher maximum body temperature within 24 h of hospitalization, longer time for virus clearance, longer duration of fever, higher levels of plasma C-reactive protein, D-dimer, procalcitonin, and aspartate aminotransferase, increased white blood cell count, particularly neutrophils, lower lymphocyte count, and higher initial viral load.

Tanner *et al*[31] performed a study on 185 hospitalized COVID-19 patients to assess the relationship between Ct value at admission and patient outcome while carefully controlling for confounders. On univariate analysis, the authors discovered that the Ct value at presentation was related to the likelihood of both ICU admission and mortality. Furthermore, Ct values changed considerably by age, length of illness at presentation, and antibody status. In a multivariate analysis, the Ct value was associated with the likelihood of death but not ICU admission. The presence of neutralizing antibodies at the time of presentation was not linked with death or ICU admission. They concluded that the SARS-CoV-2 Ct value at admission was independently related to mortality when other characteristics were controlled for and that it may be utilized for risk stratification.

SARS-COV-2 VIRAL LOAD IS NOT ASSOCIATED WITH DISEASE SEVERITY

Berastegui-Cabrera *et al*[32] conducted a prospective multicenter cohort study in 72 COVID-19 patients to assess the relationship between SARS-CoV-2 RNAemia, and viral load in the nasopharyngeal swab, and an unfavorable outcome, defined as ICU admission and/or death. Nine (12.5%) patients were treated as outpatients following an evaluation in the emergency room, whereas 63 (87.5%) patients were admitted to the hospital. Eleven (15.3%) of the patients were found to have SARS-CoV-2 RNAemia, with ten of them being hospitalized. The median viral load in plasma for the 11 SARS-CoV-2 RNAemia patients was 2.88 $\log_{10}$ copies/mL, while the median viral load in nasopharyngeal swabs for the 72 patients was 6.98 $\log_{10}$ copies/mL. Additionally, patients with SARS-CoV-2 RNAemia required more invasive mechanical ventilation (36.4% *vs* 6.6%) and had higher ICU admission rates (45.50% *vs* 8.2%) and ARDS (54.5% *vs* 9.8%). SARS-CoV-2 RNAemia patients exhibited a greater death rate (36.4% *vs* 4.9%) and a poorer prognosis (63.6% *vs* 13.1%). The authors concluded that patients with severe chronic liver disease and solid organ transplantation are more likely to have SARS-CoV-2 RNAemia at the time of the initial emergency room evaluation. They also noted that this condition is not predicted by a viral load in the upper respiratory airways and is linked to a poor prognosis.

Karahasan Yagci *et al*[33] conducted a study on 730 RT-PCR-positive patients to assess the severity of chest computed tomography (CT). Of the 284 patients admitted to the hospital, 27 (9.5%) died. There were no Ct results in 236 (32.3%) of the patients, and 216 (91.5%) of them were outpatients. In hospitalized patients, the total severity score (TSS) was much greater; 5.3% experienced severe alterations. Outpatients had lower Ct values, indicating a greater viral load. In both groups, an inverse relationship between viral load and TSS was seen. The severity of Ct was associated with age, with older individuals having a greater TSS. The authors concluded that viral load was not a significant risk factor for hospitalization or fatality. Outpatients exhibited high levels of viruses in their nasopharynx, making them infectious to their contacts. The viral load is critical in diagnosing the early stages of COVID-19 in order to limit potential transmission, whereas chest CT can assist in identifying patients that require significant medical treatment.

Le Borgne *et al*[34] conducted a retrospective study on 287 individuals with a confirmed diagnosis of COVID-19 to evaluate the association between SARS-CoV-2 viral load and disease severity. Nearly half of them (50.5%) had a moderate form, while the remaining half (49.5%) had a severe form that required mechanical ventilators. At admission, the median (interquartile range) viral load in the first upper respiratory swab was 4.76 (3.29-6.06) $\log_{10}$ copies/mL. This viral load measurement did not differ by subgroup when comparing survivors and non-survivors. Furthermore, the authors discovered that measuring respiratory viral load did not predict in-hospital mortality or disease severity. They claimed that the respiratory viral load in the first nasopharyngeal swab obtained during emergency department care is neither a predictor of the severity of the infection nor of death from SARS-CoV-2. The number of underlying comorbidities, as well as the host response to this viral infection, may be more predictive of disease severity than the virus itself.

Hasanoglu *et al*[35] studied the viral loads in six different sample types (nasopharyngeal, oral cavity, saliva, rectal, urine, and blood) from 60 patients to determine the relationship between disease severity and SARS-CoV-2 viral load, as well as differences in viral loads between asymptomatic and symptomatic patients. The authors discovered that 15 (25%) of the patients were asymptomatic, whereas 45 (75%) were symptomatic. There was a substantial difference in the mean ages of asymptomatic and symptomatic individuals (26.4 and 36.4, respectively). Asymptomatic individuals' viral loads were found to be substantially greater than symptomatic patients'. With increasing age, viral load has demonstrated a substantial negative tendency. With increasing disease severity, there was a considerable drop in viral load.

Bakir *et al*[36] conducted a study on 158 confirmed COVID-19 patients to evaluate the link between SARS-CoV-2 viral load Ct values and pneumonia. The authors discovered pneumonia in 40.5% of the individuals who underwent chest CT. SARS-CoV-2 Ct value and nasopharyngeal samples were shown to have a poor but significant connection with chest CT score. There was no link identified between viral load Ct value and age, gender, or death. There was no statistically significant relationship between chest CT score and death. The authors noted that the quantity of SARS-CoV-2 viral load did not correlate with the severity of the pulmonary lesions shown on chest CT.

Ng *et al*[37] studied 351 people (138 confirmed COVID-19 patients and 213 SARS-CoV-2-negative patients) to see if there is a link between SARS-CoV-2 viral load and disease severity. They discovered that viral loads in more seriously ill hospitalized patients, including those in the intensive care unit, were not significantly different from those in outpatient clinics. According to the authors, there is no clear association between viral load and disease severity, and a suitable biomarker for disease severity is currently unavailable in clinical settings.

DISCUSSION

Although qualitative SARS-CoV-2 RT-PCR tests are routinely used to diagnose COVID-19, the

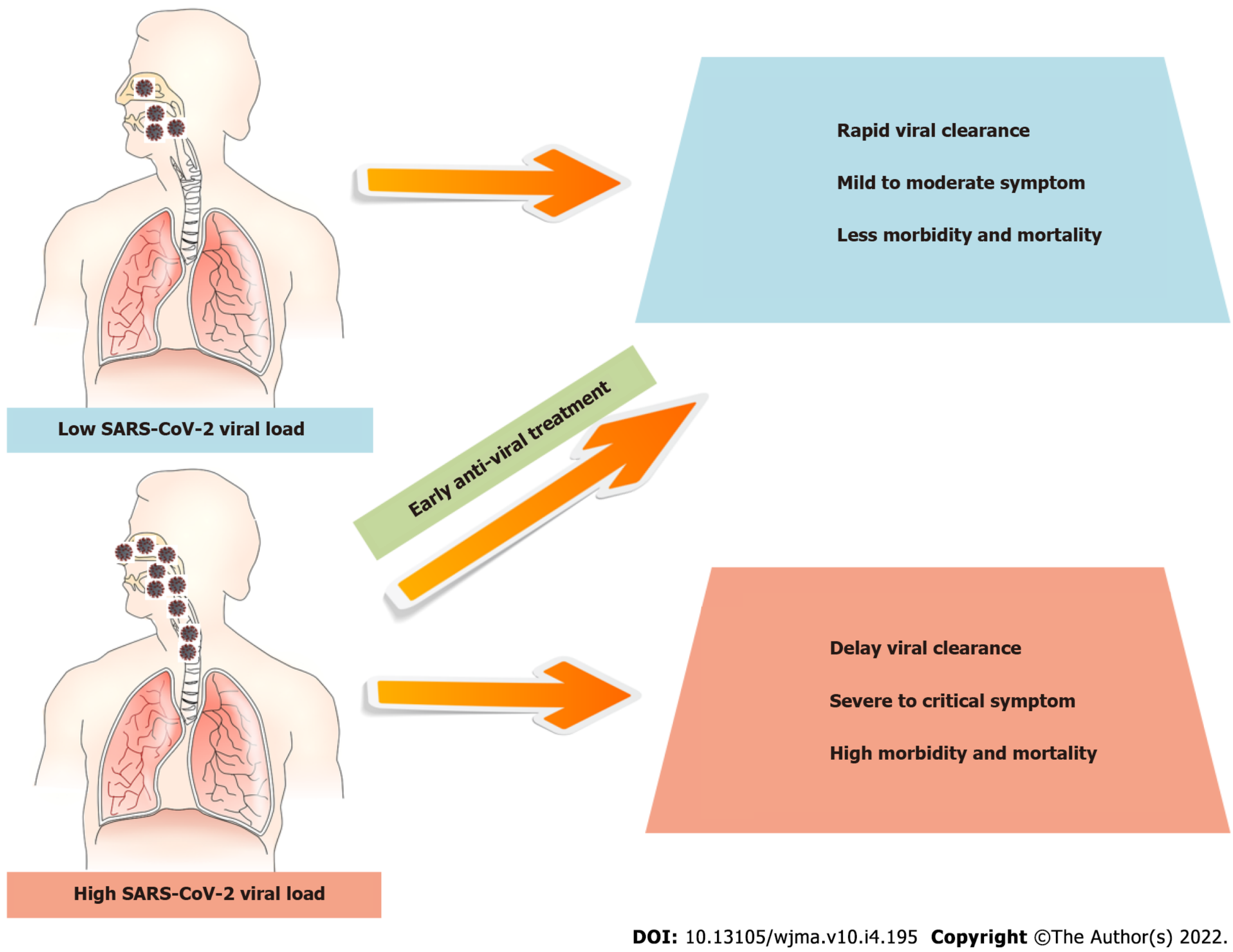

Figure 1 High and low severe acute respiratory syndrome coronavirus 2 viral load and clinical outcomes in coronavirus disease 2019 patients. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

therapeutic significance of quantitative information on Ct values being negatively associated with SARS-CoV-2 viral load for identifying viral copies must be understood. So far, several studies have shown inconsistent findings of the viral shedding kinetics in moderate and severe COVID-19 patients with an association or no association with disease severity. Table 1 summarizes the information regarding the countries of origin, study design, number of COVID-19 patients, mean or median Ct value, association of disease severity, and conclusions. The majority of the evidence suggests that a high SARS-CoV-2 viral load is associated with a severe clinical outcome. Along with this data, several studies found that patients admitted to the hospital with high SARS-CoV-2 virus loads, as determined by Ct values of nasopharyngeal swab samples, were more likely to be intubated or die during their hospitalization[11,16,38,39]. Furthermore, many researchers demonstrated that early antiviral treatment could effectively reduce virus load, shorten virus clearance time, and prevent COVID-19 from rapidly progressing to a severe disease outcome (Figure 1)[40-44].

CONCLUSION

This review demonstrates an association between the Ct value discovered in nasopharyngeal swabs, which represented the quantitative SARS-CoV-2 viral load, and COVID-19-related fatalities and disease severity in both symptomatic hospitalized and non-hospitalized patients. These findings imply that the Ct value might be utilized as a tool to aid in the identification of individuals who are at a higher risk of having a catastrophic outcome. Early antiviral medication may successfully reduce viral load, decrease virus clearance time, and prevent the fast progression of COVID-19 to severe disease outcomes in this situation.

Table 1 Severe acute respiratory syndrome coronavirus 2 viral load and disease severity in coronavirus disease 2019 patients

Ref.	Study design	No. of COVID-19 cases	Median/mean viral load (Ct or Cq) (log_{10} copies/mL)	Association with disease severity	Conclusion
Knudtzen *et al* [17], Denmark	Prospective cohort	169 (87 OP/82 IP)	24.8 *vs* 28.1 (Severe *vs* Moderate)	Yes	Lower Cq-values were found to be indicative of more disease severity in hospitalized patients
Kawasuji *et al* [18], Japan	Retrospective cohort	56 (56 IP)	5.4 *vs* 2.6 (Critical/Moderate-Severe)	Yes	The viral loads of NP swabs were correlated with disease severity and death
Maltezou *et al* [19], Greece	Prospective cohort	1122 (274 OP/848 IP)	N/A	Yes	The viral load in the nasopharynx might be utilized to identify patients at increased risk for morbidity or poor outcome
Zheng *et al*[20], China	Retrospective cohort	96 (96 IP)	N/A	Yes	The virus persists longer with higher load and peaks later in the respiratory tissue of patients with severe disease
Aydin *et al*[21], Turkey	Prospective cohort	300 (168/79/29/24)(M/I/S/C)	25.30/19.85/16.75/15.48 (M/I/S/C)	Yes	The Ct-values of saliva and oro-nasopharyngeal swab were useful in predicting disease severity
de la Calle *et al* [14], Spain	Retrospective cohort	455 (455 IP)	N/A	Yes	The Ct value of RT-PCR in nasopharyngeal swabs on admission is a useful predictive marker for the development of respiratory failure
Kwon *et al*[22], Korea	Prospective cohort	31 (31 IP)	35.2/27.9/26.7 (M/I/S+C)	Yes	High viral load in the respiratory tract and excessive cytokines and chemokines were substantially linked with the severity of COVID-19
Piubelli *et al* [23], Italy	Retrospective study	373 (373 OP)	N/A	Yes	The decreasing viral load that they observed during March to May 2020 was associated with a significant reduction in severe COVID-19 cases that needed intensive care
Shlomai *et al* [13], Israel	Retrospective cohort	170 (149 NS/21 SV)	23.43 *vs* 29.55 (NS *vs* SV)	Yes	There was a clear relationship between nasopharyngeal viral load and hypoxemia, as well as worse clinical outcomes in hospitalized COVID-19 patients
Soria *et al*[24], Spain	Prospective cohort	448 (110/236/102) (M/I/S)	35.75/32.69/29.58 (M/I/S)	Yes	The link between viral load and disease severity was shown in COVID-19 patients
Trunfio *et al* [25], Italy	Retrospective cohort	200 (32 NS/168 SV)	N/A	Yes	The Ct value detected within the first week of COVID-19 onset was associated with deaths and disease severity
Tsukagoshi *et al*[26], Japan	Retrospective study	286 (138 AS/133 SM/15 FT)	N/A	Yes	The high viral load in elderly patients at an early stage of the disease results in a bad prognosis
Wang *et al*[27], China	Prospective cohort	23 (11/12)(M/S)	N/A	Yes	The viral loads in the respiratory samples were larger in the severe group than in the mild group, and they gradually decreased with time
Faíco-Filho *et al* [28], Brazil	Retrospective cohort	875 (439/266/170)(M/I/S)	22/27/21.5 (M/I/S)	Yes	The SARS-CoV-2 virus load at admission was independently linked with death among hospit-alized COVID-19 patients
Pérez-García *et al*[29], Spain	Retrospective study	255 (85/87/83) (M/I/S)	N/A	Yes	The SARS-CoV-2 viral load was a risk factor, but CCL5 was a protective factor for ICU admission or mortality during hospitalization
Guo *et al*[30],	Prospective	195 (16/132/41/6)	33.74/33.59/32.10/27.53	Yes	The higher initial viral load was

China	cohort	(M/I/S/C)	(M/I/S/C)		associated with disease severity in COVID-19 patients
Tanner *et al* [31], United Kingdom	Prospective cohort	185 (IP)	N/A	Yes	The SARS-CoV-2 Ct value at admission was independently related with mortality
Berastegui-Cabrera *et al* [32], Spain	Prospective cohort	72 (9 OP/63 IP)	N/A	No	The viral load in the upper respiratory airways was associated with poor outcome
Karahasan Yagci *et al*[33], Turkey	Retrospective study	730 (446 OP/284 IP)	(27.8/29.4/27.9) (M/I/S)	No	The viral load was not a significant risk factor for hospitalization or fatality
Le Borgne *et al* [34], France	Retrospective study	287 (42 NS/245 SV)	4.99 *vs* 4.76 (NS *vs* SV)	No	The viral load in the first nasopharyngeal swab was neither a predictor of severity nor of death in SARS-CoV-2 infection
Hasanoglu *et al* [35], Turkey	Prospective cohort	60 (15 AS/45 SM)	N/A	No	Asymptomatic individuals' viral loads were found to be substantially greater than symptomatic patients'
Bakir *et al*[36], Turkey	Retrospective study	158 (45 OP/113 IP)	26.76 *vs* 27.53 (OP *vs* IP)	No	The quantity of SARS-CoV-2 viral load did not correlate with the severity of the pulmonary lesions shown on chest CT
Ng *et al*[37], USA	Retrospective study	133	N/A	No	The viral loads in more seriously ill hospitalized patients were not significantly different from those in outpatient clinics

AS: Asymptomatic; C: Critical; CCL5: Chemokine (C-C motif) ligand 5; Cq: Cycle quantification; Ct: Cycle threshold; CT: Computerized tomography; FT: Fatality; I: Intermediate; IP: Inpatient; M: Mild; N/A: Not applicable; NP: Nasopharyngeal; NS: Non-survivor; OP: Outpatient; RT-PCR: Reverse transcription polymerase chain reaction; S: Severe; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SM: Symptomatic; SV: Survivor.

FOOTNOTES

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META-ANALYSIS

No increase in burnout in health care workers during the initial COVID-19 outbreak: Systematic review and meta-analysis

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Abstract

BACKGROUND

For decades and before the coronavirus disease 2019 (COVID-19) pandemic, for health care workers (HCWs) burnout can be experienced as an upsetting confrontation with their self and the result of a complex a multifactorial process interacting with environmental and personal features.

AIM

To literature review and meta-analysis was to obtain a comprehensive understanding of burnout and work-related stress in health care workers around the world during the first outbreak of the COVID-19 pandemic.

METHODS

We performed a database search of Embase, Google Scholar and PubMed from June to October 2020. We analysed burnout risk factors and protective factors in included studies published in peer-reviewed journals as of January 2020, studying a HCW population during the first COVID-19 wave without any geographic restrictions. Furthermore, we performed a meta-analysis to determine overall burnout levels. We studied the main risk factors and protective factors related to burnout and stress at the individual, institutional and regional levels.

RESULTS

Forty-one studies were included in our final review sample. Most were cross-sectional, observational studies with data collection windows during the first wave of the COVID-19 surge. Of those forty-one, twelve studies were included in the meta-analysis. Of the 27907 health care professionals who participated in the reviewed studies, 70.4% were women, and two-thirds were either married or living together. The most represented age category was 31-45 years, at 41.5%. Approximately half of the sample comprised nurses (47.6%), and 44.4% were working in COVID-19 wards (intensive care unit, emergency room and dedicated internal medicine wards). Indeed, exposure to the virus was not a leading factor for burnout. Our meta-analytic estimate of burnout prevalence in the HCW population for a sample of 6784 individuals was 30.05%.

CONCLUSION

There was a significant prevalence of burnout in HCWs during the COVID-19 pandemic, and some of the associated risk factors could be targeted for intervention, both at the individual and organizational levels. Nevertheless, COVID-19 exposure was not a leading factor for burnout, as burnout levels were not notably higher than pre-COVID-19 levels.

Key Words: Burnout; Initial COVID-19 outbreak; SARS-CoV-2 pandemic; Healthcare workers; Mental health services; Maslach burnout inventory

Core Tip: We performed a database search from June to October 2020. We analysed burnout risk factors and protective factors in retained studies and performed a meta-analysis to determine overall burnout levels during the initial coronavirus disease 2019 (COVID-19) outbreak. We found a significant prevalence of burnout in health care workers during the COVID-19 pandemic and some of the associated risk factors could be targeted for intervention, both at the individual and organizational level. Nevertheless, COVID-19 exposure was not a leading factor for burnout, as burnout levels were not notably higher than pre-COVID-19.

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INTRODUCTION

Burnout is an occupational phenomenon defined as a syndrome of emotional exhaustion, depersonalization of others, and a feeling of reduced personal accomplishment[1,2]. It is the result of a complex and multifactorial process, with interacting environmental features and personal frailties[3-6], in a process that juxtaposes personal needs and expectations on one hand, and the institution's demands, (in)equalities and (in)justices on the other. For health care workers (HCWs), burnout can be experienced as an upsetting personal confrontation, as the progressive lack of compassion and diminished effectiveness has a distressing impact on their professional identity[4]. The scientific literature on HCW burnout is vast, as decades before the coronavirus disease 2019 (COVID-19) pandemic, burnout was recognized as a significant problem both in terms of magnitude and impact. A recent systematic review over a period of 25 years showed burnout levels of 25% among nurses[7]. Another recent meta-analysis studying physicians reported a combined prevalence of 21%, although with substantial variability due to uneven definitions, assessment methods, and study quality[8]. In the past decade, an increasing number of respiratory virus epidemics have placed additional pressure on the health care system and its workers through various mechanisms. During the 2003 severe acute respiratory syndrome (SARS) outbreak, some HCWs isolated themselves out of fear of infecting their friends and families[9], and lack of training, protection and hospital support was associated with higher burnout[10]. The novel influenza A virus (H1N1) outbreak in 2009 highlighted HCWs' concern for infection of family and friends and fears about consequences for their own health[11]. Other authors showed an increase in the stress and psychological burden of HCWs during the 2012 Middle East Respiratory Syndrome outbreak, due to infectious disease-related stigma, such as social rejection or discrimination[12], or increased burnout levels due to poor hospital resources[13].

Early 2020, economic uncertainty and societal anxiety reached unseen levels, as the COVID-19 pandemic profoundly changed our view of health, work and social interactions. As the UN put it, we are facing a global health crisis […], one that is killing people, spreading human suffering, and upending people's lives. However, this is much more than a health crisis. It is a human, economic and social crisis[14]. For most workers, the pandemic has accelerated a change in workplace habits and a shift from office work towards teleworking. HCWs, however, were subject to sudden and dramatic transformation of the health care institutions and were faced with unseen numbers of critically ill patients and casualties. In many countries, the pandemic was source of a tremendous increase in workload and significant levels of stress and fear regarding physical integrity. Most countries were faced with an ominous atmosphere of fear of the unknown and a staggering shortage of means, including personal protective equipment (PPE). Particularly in the early days of the pandemic, HCWs were facing uncertainty about the virus's modes of transmission, questions about levels of contagiousness, and hence about the risk of self-infection and of infecting family members and friends.

Burnout in HCWs has been associated with poor patient safety outcomes, medical errors and adverse outcomes on the health care system as a whole[15,16]. In this review, we explore the main contributors to burnout in health care providers, specifically within the scope of the COVID-19 pandemic in early 2020. Despite the great variability in burnout measuring instruments, subscales, and cut-off levels therein, we endeavour to provide a meta-analytic estimate of burnout levels during the initial COVID-19 outbreak.

MATERIALS AND METHODS

Database search and initial study selection

We conducted a literature search in PubMed, Embase and Google Scholar from 1st of June to 10th of October 2020, following the PRISMA 2020 recommendations (unregistered). The search terms were associated with Boolean operators as detailed in Supplementary Table 1. Some additional relevant articles were included from the references sections of the articles found in the initial search.

Study eligibility criteria

We included original studies published in peer-reviewed journals as of January 2020, studying an HCW population during the first COVID-19 wave without any geographic restrictions. The exclusion criteria are detailed in Table 1. Initially, assessed studies comprised several randomized controlled trials (RCTs), mostly cross-sectional and some interventional studies. From those, RCTs and interventional studies were excluded during the screening phase, as they were not within the burnout or stress scope of this review.

Independent variables

The main independent variable was burnout and its prevalence during the COVID-19 pandemic in the first half of 2020 as measured with a recognized instrument or validated custom instrument. High levels of chronic work-related stress are generally accepted as a precipitator of burnout, and a recent study showed that high stress levels interfere with sound sleep[17], which in turn can precipitate burnout. Taking this into consideration, we included (perceived) stress as an independent variable in our analysis.

The main instrument used is the Maslach Burnout Inventory (MBI), a scale measuring burnout through three dimensions: emotional exhaustion (EE), depersonalization (DP) and decreased personal achievement (PA)[18,19]. EE refers to feelings of being overextended and depletion of one's resources [6]. Conceptually, it incorporates traditional stress reactions, such as job-related depression, psychosomatic complaints and anxiety[20,21], and has been related to similar behavioural outcomes, such as intention to quit and absenteeism[22]. HCWs experiencing EE feel apathetic and indifferent about their work and patients and no feel longer invested in situations arising during their workday[23]. DP refers to a cynical, insensitive, or disproportionately detached response to other people as EE becomes more severe. It can be perceived as withdrawal or mental distancing from care recipients[24], which are distancing techniques used to reduce the intensity of arousal and prevent the worker from disruption in critical and chaotic situations requiring calm and efficient functioning[25]. PA refers to a decline in one's feelings of competence and successful achievement at work, reduced productivity, low morale and inability to cope[26]. One can appreciate how reduced performance and productivity among HCWs lead to poor clinical decision-making and medical errors[23]. The questions used in the MBI are detailed in Supplementary Table 2. Other instruments used are detailed in Supplementary Table 3.

Dependent variables

The dependent variables were sociodemographic variables, personality traits, psychological and physical health status, occupational role, ward, organizational and geographic variables. Physical symptoms were described in certain studies, but they were not the focus of this review. The detailed study selection process is outlined in the flow chart in Figure 1.

Statistical analysis and meta-analysis

Units were unified for aggregation of dependent variables. When only median age and standard deviation were available, we used normal distribution inference to categorize the respondents into age categories. For other studies, we forced study age groups in the closest comparable group of our review. These adaptations may report inaccurate age distributions at the individual study level, but we believe that the aggregated data benefit from this approach. Meta-analysis was performed in MedCalc Version 19.5.3. Proportions with random effects models were studied, and we calculated the I^2 statistic of hetero-

Table 1 Exclusion criteria for the qualitative review

Studies that did not unambiguously study burnout and/or stress at work
Studies that did not focus on HCWs or a subpopulation thereof
Literature reviews, meta-analyses and systematic reviews
Full English text not available
Preprints, unreviewed articles
Short communications, editorials, *etc*. (not sufficient data)

HCWs: Health care workers.

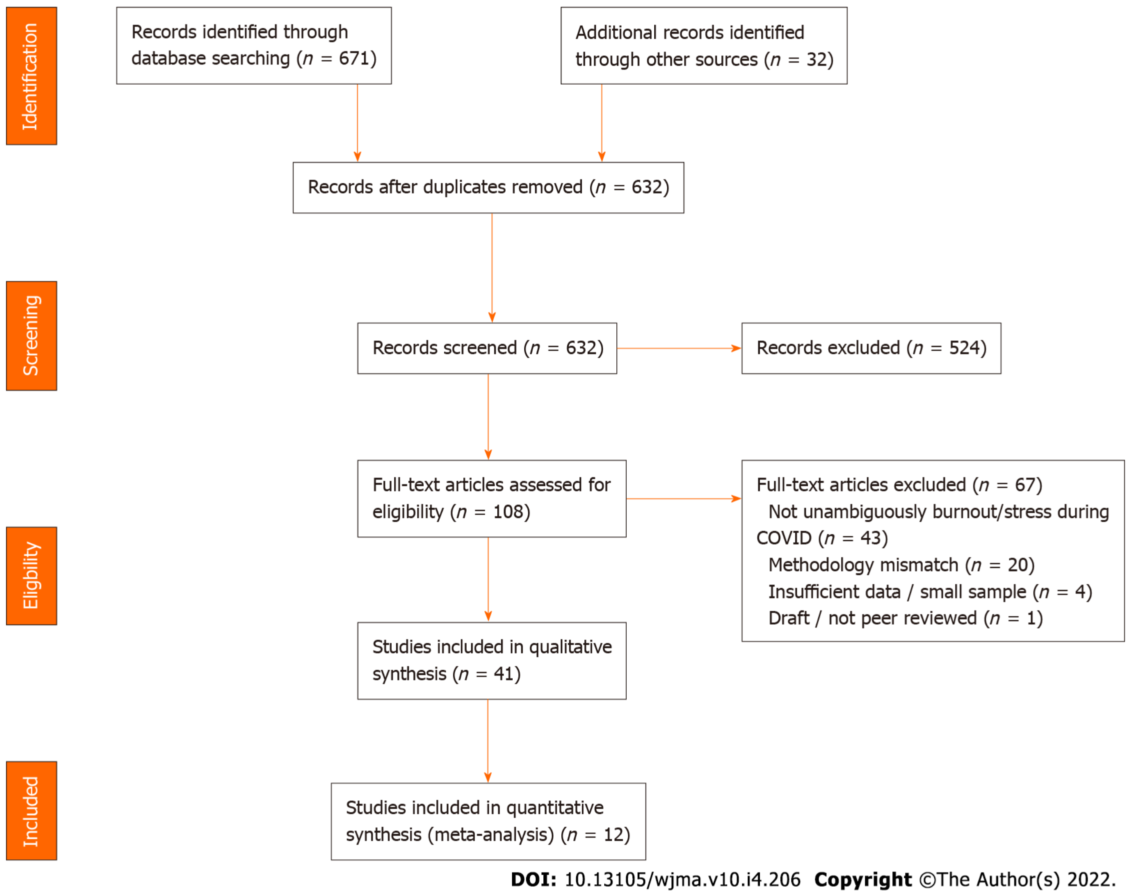

Figure 1 Flow chart of the selection process.

geneity and publication bias through Egger's and Begg's tests, respectively.

Review outcomes

From the final list of retained studies, we selected those that had sufficient numeric data to perform a meta-analysis. These studies used validated burnout measuring instruments and reported either burnout prevalence or scores that permitted deducing HCW burnout prevalence. Descriptive analysis was performed using statistically significant data from the studies retained. For some studies, the conclusions retained in our review may not have been the most striking outcomes from their perspective. We focused mainly on burnout, stress, and related dependent variables.

RESULTS

Features of the included studies and sociodemographic data

Through screening, 39 cross-sectional, one longitudinal and one prospective cohort study were retained.

Of the 41 studies, all from 2020, 12 were included in the meta-analysis. Table 2 details the main features of the studies.

Of the studies retained, 44% were European studies, and 28% studied Asian-Pacific countries. After China, the pandemic hit hardest in European countries, such as Italy and Spain, in the first quarter of 2020. These two countries represented 21% and 19% of the respondents of European studies, respectively. Among the latter, Germany represented 39%. Table 3 shows a sociodemographic overview of respondents in the 41 studies. Of the 27907 health care professionals who participated in the reviewed studies, 70.4% were women, and two-thirds were either married or living together. The most represented age category was 31-45 years, at 41.5%. Approximately half of the sample comprised nurses (47.6%), and 44.4% were working in COVID-19 wards [intensive care unit (ICU), emergency room (ER) and dedicated internal medicine wards]. Supplementary Table 4 displays the complete list of studies and, for each study, a short description summarizing the main conclusions relevant for our review.

Burnout prevalence and meta-analytic estimate

Twelve studies were included in our meta-analysis (Figure 2). Egger's test result was -3.7859 (95%CI: -11.79–4.22 and P = 0.3169), and Begg's test rendered a Kendall's Tau of -0.1818 (P = 0.4106), showing no significant asymmetry or publication bias. The test for heterogeneity, however, showed a high level of inconsistency (I^2: 96.66%, P < 0.0001), prompting the use of the random effects model in estimating the meta-analytic effect. The meta-analytic estimate of burnout prevalence in HCWs was 30.05% (95%CI: 23.91%–36.5%), with a sample size of 6784.

DISCUSSION

The typical profile of an HCW with high levels of burnout was a single female nurse or resident physician under 30 years of age in an institution perceived as poorly prepared for the COVID-19 pandemic. This HCW experienced anxiety regarding infection with COVID-19 or infecting their friends and family and might have had a history of prior psychiatric conditions and low levels of resilience.

Age, sex, marital status

A recurring risk factor associated with burnout was female sex[27-34]. Female sex was correlated with higher perceived stress[17,35-38], despite one study showing identical cortisol levels as in males. This is consistent with males being less likely to report symptoms, even if they were experiencing them[29,30], and with females having a higher tendency to somatise[34].

Early residency years and younger age were associated with higher stress levels, burnout and associated negative symptoms[17,29-31,35,40-42]. Younger physicians are more likely to have young children, which may explain the increased stress of infecting families. Accordingly, one study found higher perceived stress levels in HCWs with small children[43]. In nurses, the number of children and parenting stress were positively correlated with burnout[44]. Some authors stated that senior residents experienced more stress because of the inability to quickly adapt to a new subject they never learned in medical school[45]. Among nonphysicians, younger HCWs had lower levels of burnout than middle-aged groups[46], although other authors found that more experience comes with less burnout[47].

Single respondents experienced higher burnout than those who were married or in a relationship[36,44]. Respondents with support from family and friends scored lower on stress and burnout[34-36,48], whereas living alone predicted increased stress[49]. We believe that social support could be considered an external resource that alleviates burnout, fitting the Job Demands-Resources (JD-R) burnout model [24].

Health status, coping strategies, resilience

Prior psychiatric conditions were strongly correlated with high levels of burnout and distress[29,48]. Higher levels on the EE and DP subscales were linked with more negative symptoms[28,42], including irritability, change in food habits, insomnia, depression and muscle tension[50]. Similarly, reporting physical symptoms was associated with higher stress levels[51], although this association may be bidirectional[52]. Additionally, an association was found between EE and the perception of needing psychiatric treatment in the future[53].

A positive attitude was strongly protective against stress, whereas avoidance constituted a risk factor [36,49]. Stigma (discrimination, fear of COVID-19) was an important predictor of burnout[33]. Resilience was associated with lower levels of stress, anxiety, fatigue, and sleep disturbances[54], as well as less COVID-19-related anxiety[55], symptoms of posttraumatic stress and depression[42] and burnout[44]. Resilience is a complex coping mechanism in which individuals can function in difficult environments. Focusing on solutions rather than on difficulties puts the individual in a position that favours the development of new skills[56,57].

Table 2 Main features of the studies selected (N = 41)

	N	%		N	%
Publication month (2020)			**Region**		
March	1	2	Asia & Pacific	12	29
April	3	7	Europe	18	44
May	3	7	Global	2	5
June	5	12	Middle east	3	7
July	3	7	North America	4	10
August	15	37	South/Latin America	2	5
September	6	15			
October	5	12	**Population**		
			Physicians	36	88
Type of work			Nurses	27	66
Cross-sectional survey	39	95	Other HCWs	17	41
Longitudinal study	1	2			
Longitudinal cohort study	1	2	**Measuring scale**		
			Validated burnout scale	18	44
			Validated stress scale	18	44

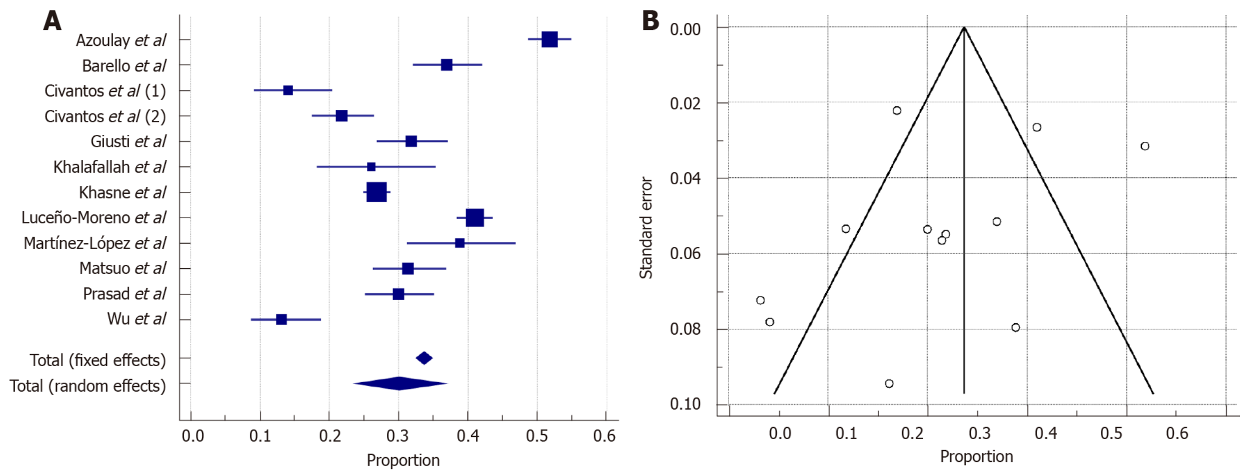

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Figure 2 Studies included in meta-analysis. A: Forest plot of studies; B: Funnel plot of studies.

Occupational role, ward, contact with COVID-19 patients

Several authors reported higher levels of stress or burnout in nurses than in physicians or other HCWs [38,41,43,46,51,58]. Several authors who studied the nurse population highlighted the importance of organizational support, safety guidelines, and PPE as protective from burnout related to anxiety about self-infection or infection of friends and families[32,34,55,59]. Some authors found that nurses had high morale, enthusiasm and empathy, which could partially set off burnout along the DP axis[47]. Despite having similar stress levels to physicians and working in equally difficult situations in terms of the availability of resources, nurses scored higher compassion satisfaction (CS), which protects against burnout[60].

There is an important intersection between nurses and the female population; women accounted for 93.2% among four studies studying only nurses, making female sex an important confounding factor. In many cultures, women are still in charge of the household and the children, often causing a surplus in workload and obligations. The nursing population had to deal with increased workload at work and locked-down children who needed to be fed and protected from infection. Additionally, nurses spending the most time with patients are most vulnerable to the risk of infection if PPE is lacking.

Table 3 Sociodemographic data of the respondents of studies reviewed

	N							%
Region	**Asia & Pacific**	**Europe**	**Middle east**	**North America**	**South/Latin America**	**Multi-country**	**Total**	
Studies	12	18	3	4	2	2	41	
Respondents	12587	9754	1774	1546	512	1734	27907	
%	45.1	35.0	6.4	5.5	1.8	6.2		
Gender[a]								
Female	9775	6590	1176	544	179	342	18606	70.4
Male	2695	3'073	598	339	333	659	7697	29.1
Non-binary/other	37	91	0	1	0	0	129	0.5
Age category[b]								
18-30	5344	1767	430	407	94	397	8439	30.7
31-45	5134	3543	1157	676	249	639	11398	41.5
> 45	2078	4019	187	460	169	699	7612	27.7
Occupational role								
Physician	3308	3780	799	1134	512	1734	11267	40.4
Nurse	7996	4499	552	248	0	0	13295	47.6
Other	1283	1475	423	164	0	0	3345	12.0
Ward[a]								
Front line	5336	2931	860	947	0	1001	11075	44.4
Usual ward	7251	4212	914	252	512	733	13874	55.6
Married/concubine[a]								
Yes	5704	2624	987	92	-	831	10238	66.2
No	3691	1204	149	19	-	170	5233	33.8
Children[a]								
Yes	515	1086	277	185	-	0	2063	48.6
No	905	778	149	352	-	0	2184	51.4
Psychological comorbidities[a]								
Yes	-	45	122	-	18	0	185	9.2
No	-	675	1013	-	145	0	1833	90.8

[a]Not all studies delivered this information.

[b]Some respondents were forced in these categories based on normal distributions.

Interestingly, a few studies found that whether HCWs dealt directly with COVID-19 patients did not correlate with burnout or stress[51,61], possibly because it was counterbalanced by higher CS[62]. For others, the actual duration of interactions with COVID patients was associated with a higher risk of burnout[17,48,61]. In ICUs around the world, direct COVID-19 exposure was not a leading factor for burnout[27]. Some authors found that working with COVID-19 patients increased stress[31,36-38,54,63,64]. Others found the opposite: lower burnout levels in front-line wards (FL) compared to usual wards (UW)[65,66]. The number of positive cases in the country was not associated with burnout or stress[46,67]. Some authors stated that redeployed staff had a higher risk of burnout, possibly related to increased demands, limited resources, and psychological stress of dealing with an unfamiliar disease in an unfamiliar environment[40]. Others found that redeployment had no impact on perceived stress[59]. One study found that surgical residents had a decrease in routine surgical activities along with a decrease in burnout[68].

The predominant theory appears to be that FL workers were subject to less burnout than UW workers. We postulate that FL had more opportunity to exercise competencies and judgement, thereby increasing their sense of control. From the Job Strain-Job Decision model perspective, this put these workers in active jobs, with higher job satisfaction and actual development of competencies, setting off part of the higher stress (*vs* UW) and generating new behaviour patterns[69]. Accordingly, Dinibutun [70] found a high sense of PA among physicians in FL. We also suggest that FL workers experienced increased attention from hospital management, with more communication and updated policies. FL workers received public and media recognition, increasing their sense of worth, experienced by some as justice, at last. Several burnout models appreciate that recognition and sense of worth act as enhancers of rewards, alleviating high efforts[71,72] as somehow protective from burnout.

In primary care, some authors measured lower levels of psychological distress, possibly explained by the use of telemedicine, alleviating the risk of infection[73]. We believe, however, that unprepared implementation of technological diagnostic tools can also lead to technostress. This is suitably illustrated by a global study amongst dermatologists who started using telemedicine during the COVID-19 pandemic[50].

Organizational and geographic factors

Higher actual or perceived preparedness at the hospital or country level was associated with lower stress or burnout[27,43,50,53,58,59]. Underlying features of preparedness included availability of PPE, training, communication, and protocols; improving these could alleviate perceived stress[58,74,75]. Increased stress and burnout related to preparedness was partially mediated by fear of self-infection and infection of others[32,48,50,52,59]. Increased appreciation and communication from hospital management was correlated with less burnout[74], whereas institutional failure to triage appropriately, or a lack of ethical climate increased stress and burnout[27]. Having been tested for COVID-19 or sufficient and discretionary access to testing for patients seemed protective from burnout[74]. Conversely, having infected relatives could significantly increase stress[34].

Preparedness is a textbook illustration of burnout models in action. The unavailability of resources (such as PPE) to accomplish one's job in the best possible conditions increases disengagement and DP, as postulated in the JD-R model[24,53], increases strain through anxiety of transmitting the virus[69] and decreases resources through social isolation (to avoid transmission)[24]. Lack of institutional communication and protocols are decreased reward components in the Effort-Reward Imbalance model: they create job and institutional uncertainty[71] and might be perceived as unjust by the worker[72].

Burnout prevalence

According to several pre-COVID-19 meta-analyses, burnout prevalence among residents was 35.7%[76] or above 60%[77]. Among nurses, burnout prevalence was between 15% and 28%[78], between 29% and 36%[79] and between 15% and 35%[80]. The pooled prevalence of a 2020 meta-analysis among 1943 emergency physicians was between 35% and 41%[81]. Our own meta-analytic estimate of burnout during the first wave of the COVID-19 pandemic was approximately 30%, *i.e.*, less than most studies pre-COVID-19. We hypothesize that, although HCWs were put under enormous strain during this period, they were also rewarded by a considerable increase in attention and had the opportunity to give actual sense to their profession, albeit in very difficult circumstances. Additionally, we must put this number in perspective, as it is based on very different studies in terms of duration, methodology and geography.

Limitations

The short time span of a pandemic does not necessarily allow for the time and preparation needed to set up a well-structured randomized controlled trial. This may explain the lack of many such studies and their subsequent absence in our review. Cross-sectional studies, in contrast, do not admit explanation by causality. The absence of a control group in cross-sectional studies does not allow us to determine if findings are reflective of the general population or only of considered HCWs.

Responder bias and auto-questionnaires are important limitations of cross-sectional studies. Certain topics, such as a prior history of psychiatric conditions, are particularly at risk of response bias given the possible stigma. Additionally, at the time of the survey, HCWs might not have been interested due to a lack of any personal (mental) health concerns, or conversely, they could have been suffering from a crushing burden of either stress, burnout, or physical symptoms, preventing them from responding to the survey.

Another limitation of this review is that, during this pandemic, we must consider that occupational burnout could have been caused by the interaction between environmental-related (such as workplace-related events) and individual-related factors (such as disruption of work–life balance and personality traits)[81].

Limitations specific to our review and meta-analysis are the heterogeneity of studies in terms of measurement instruments, scales and subscales, and cut-off scores used to determine overall burnout prevalence. There was also geographic diversity and heterogeneity of the populations studied, as our intention was not to focus on one part of the workforce or region but to highlight burnout and its influencing factors in the specific context of the COVID-19 pandemic. As a result, we cannot compare the prevalence of our study with the prevalence found in earlier, pre-COVID-19 studies.

Relevance to clinical practice

It is critical that countries and institutions understand and acknowledge the nature, risk factors and protective factors of stress and burnout in their health care workforce. Awareness lies at the basis of preventive interventions, which can happen both at the individual and institutional levels.

In a pandemic context such as COVID-19, specific interventions could probably yield immediate results, benefiting HCWs and patients in very direct ways. We have highlighted how institutional preparedness has a clear correlation with stress and burnout. PPE, up to date protocols, and regular communication from hospital management are low hanging fruit, as they would both reduce actual infection rates amongst staff and alleviate fear of infection and transmission. Workload and stress about childcare are recurring subjects, and if the former is a challenge during a pandemic, it should be feasible for institutions to help organise childcare for single workers who are more at risk for burnout.

Commonly studied burnout interventions in HCWs are mindfulness, stress management and small-group discussions. The results suggest that these factors could have positive effects on burnout, although more research is needed[82]. A recent mapping by Hilton *et al*[83] of RCTs conducted in health care providers and medical students returned promising results on the use of mindfulness in the workplace but highlighted the need for more definitive evidence of benefits on burnout. Other interventions focus on leadership skills, community and institutional culture, which have been largely studied[84,85].

Where prevention fails, institutions must deal with existing stress and burnout resulting from both ordinary and extraordinary circumstances. Some institutions implemented telephone helplines for HCWs with difficulties coping with grief, death, high workloads, and burnout, the use of which was perceived as useful and appropriate[86,87]. A culture promoting acknowledgement, communication and peer support programs, employee assistance programs and structured health response programs are many other exploration options.

CONCLUSIONS

During the COVID-19 pandemic, HCWs have been under high levels of stress and have suffered considerable burnout, putting quality of care at risk. We reviewed 41 studies and highlighted personal and sociodemographic features strongly associated with higher perceived stress and burnout. Female sex, younger age, low resilience, nurse occupational role and lack of preparedness were associated with higher burnout, but actual COVID-19 exposure was not a leading factor. Prevalence pre-COVID-19 was either lower or in the same ballpark as during COVID-19; our meta-analytic estimate based on 12 studies and approximately 6800 respondents returned a burnout prevalence of 30%, with important geographical variations. Both the individual and macro levels offer opportunities for intervention, as primary and secondary prevention, but the identification of early signs could also inform a reduction in burnout levels in our health care workforce. Further research is needed to evaluate the mid- and long-term impacts of the COVID-19 outbreak on HCWs.

ARTICLE HIGHLIGHTS

Research background

For decades and before the coronavirus disease 2019 (COVID-19) pandemic, for health care workers, (HCWs) burnout can be experienced as an upsetting confrontation with their self and the result of a complex a multifactorial process interacting with environmental and personal features.

Research motivation

During these century previous outbreak, some HCWs isolated themselves out of fear of infecting their friends and families, and lack of training, protection and hospital support was associated with higher burnout.

Research objectives

The objective of this literature review and meta-analysis was to obtain a comprehensive understanding of burnout and work-related stress in health care workers around the world during the first outbreak of the COVID-19 pandemic.

Research methods

We analysed burnout risk factors and protective factors in included studies published from June 1, 2020 to October 10, 2020, studying an HCW population during the first COVID-19 wave. The typical profile of an HCW with high levels of burnout was a young, single, female nurse or resident physician in an institution perceived as poorly prepared for the COVID-19 pandemic. This HCW experienced anxiety related to infection with COVID-19 or infecting her friends and family and possibly had a history of prior psychiatric conditions and low levels of resilience. Nevertheless, COVID-19 exposure was not a leading factor in burnout, as burnout levels were not notably higher than those before the COVID-19 pandemic. We included original studies published in peer-reviewed journals as of January 2020, studying an HCW population during the first COVID-19 wave without any geographic restrictions

Research results

Through screening, 39 cross-sectional, one longitudinal and one prospective cohort study were retained. Of the 41 studies, all from 2020, 12 were included in the meta-analysis. Table 2 details the main features of the studies. Of the 27907 health care professionals who participated in the reviewed studies, 70.4% were women, and two-thirds were either married or living together. The most represented age category was 31-45 years, at 41.5%. Approximately half of the sample comprised nurses (47.6%), and 44.4% were working in COVID-19 wards (intensive care unit, emergency room and dedicated internal medicine wards). The meta-analytic estimate of burnout prevalence in HCWs was 30.05% (95%CI: 23.91%–36.5%), with a sample size of 6784.

Research conclusions

During the COVID-19 pandemic, HCWs have been under high levels of stress and have suffered considerable burnout, putting quality of care at risk. We reviewed 41 studies and highlighted personal and sociodemographic features strongly associated with higher perceived stress and burnout. Female sex, younger age, low resilience, nurse occupational role and lack of preparedness were associated with higher burnout, but actual COVID-19 exposure was not a leading factor. Prevalence pre-COVID-19 was either lower or in the same ballpark as during COVID-19; our meta-analytic estimate based on 12 studies and approximately 6800 respondents returned a burnout prevalence of 30%, with important geographical variation

Research perspectives

In a pandemic context such as COVID-19, specific interventions could probably yield immediate results, benefiting HCWs and patients in very direct ways. We have highlighted how institutional preparedness has a clear correlation with stress and burnout. PPE, up-to-date protocols and regular communication from hospital management are low hanging fruit, as they would both reduce actual infection rates amongst staff and alleviate fear of infection and transmission. Workload and stress about childcare are recurring subjects, and if the former is a challenge during a pandemic, it should be feasible for institutions to help organize childcare for single workers who are more at risk for burnout. Where prevention fails, institutions must deal with existing stress and burnout resulting from both ordinary and extraordinary circumstances. Some institutions implemented telephone helplines for HCWs with difficulties coping with grief, death, high workloads, and burnout, the use of which was perceived as useful and appropriate. A culture promoting acknowledgement, communication and peer support programs, employee assistance programs and structured health response programs are many other exploration options.

FOOTNOTES

Author contributions: Kimpe V helped to develop the research question, performed the review, and wrote the main part of the manuscript; Sabe M participated in the development of the research question, helped with the meta-analysis strategy and contributed to the writing of the manuscript; Sentissi O developed the research question, oversaw the progress of the review, and contributed to the writing of the manuscript. The authors approved the manuscript.

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Abstract

BACKGROUND

Studies to date comparing outcomes of microwave ablation (MWA) with radiofrequency ablation (RFA) on patients with hepatocellular carcinoma have yielded conflicting results, with no clear superiority of one technique over the other. The aim of this systematic review and meta-analysis was to compare the efficacy and safety of MWA with RFA.

AIM

To perform a systematic review and meta-analysis comparing the efficacy and safety of MWA with RFA.

METHODS

A systematic literature search was performed using Ovid Medline, Embase, PubMed, Reference Citation Analysis, Cochrane Central and Cochrane Systematic Review databases, and Web of Science. Abstracts and full manuscripts were screened for inclusion utilising predefined inclusion and exclusion criteria comparing outcomes of MWA and RFA. A random-effects model was used for each outcome. Meta-regression analysis was performed to adjust for the difference in follow-up period between the studies. Primary outcome measures included complete ablation (CA) rate, local recurrence rate (LRR), survival [local recurrence-free survival (LRFS), overall survival (OS)] and adverse events.

RESULTS

A total of 42 published studies [34 cohort and 8 randomised controlled trials (RCT)] with 6719 patients fulfilled the selection criteria. There was no significant difference in tumour size between the treatment groups. CA rates between MWA and RFA groups were similar in prospective cohort studies [odds ratio (OR) 0.95, 95% confidence interval (CI) 0.28–3.23] and RCTs (OR 1.18, 95%CI 0.64–2.18). However, retrospective studies reported higher rates with MWA (OR 1.29, 95%CI 1.06–1.57). Retrospective cohort studies reported higher OS (OR 1.54, 95%CI 1.15–2.05 and lower LRR (OR 0.67, 95%CI 0.51–0.87). No difference in terms of LRFS or 30-d mortality was observed between both arms. MWA had an increased rate of adverse respiratory events when compared to RFA (OR 1.99, 95%CI 1.07–3.71, P = 0.03).

CONCLUSION

MWA achieves similar CA rates and as good or better longer-term outcomes in relation to LRR and OS compared to RFA. Apart from an increased rate of respiratory events post procedure, MWA is as safe as RFA.

Key Words: Microwave ablation; Radiofrequency ablation; Hepatocellular carcinoma; Survival; Recurrence; Meta-analysis

Core Tip: Studies to date comparing outcomes of microwave ablation with radiofrequency ablation have yielded conflicting results, with no clear superiority of one technique over the other. To our knowledge, this is the most comprehensive study on this topic. A large cohort of 6719 patients were examined, enabling us to identify outliers and provide results with a smaller margin of error. The primary outcomes of this study were complete ablation, local recurrence rate, overall and local recurrence free survival and safety.

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INTRODUCTION

Hepatocellular carcinoma (HCC) now ranks worldwide as the seventh most common cancer and the second leading cause of cancer mortality[1-3] and is rapidly increasing in incidence in several developed regions including North America, Europe, and Australasia[4-6]. Furthermore, an increasing proportion of HCC patients are being diagnosed at an early stage and are eligible for curative therapy[7,8] including local ablation which is considered standard of care for those not suitable for surgery[9-11].

Of the common modalities used to ablate HCC, radiofrequency ablation (RFA) is the most strongly recommended[12]. This is based on evidence from randomised controlled trials (RCTs)[13-16] and three meta-analyses[17-19] showing that RFA provides better local disease control and overall survival (OS) outcomes than percutaneous ethanol injection, particularly among nonsurgical candidates[20]. Recently, microwave ablation (MWA) has become a popular ablative technique because of its reduction in heat-sink effect, ability to produce wider and more predictable ablation volumes that result in high complete ablation rates, and the ability to simultaneously treat multiple and/or larger lesions more effectively and over a shorter procedural time[12,21]. Studies to date comparing outcomes of MWA with RFA have yielded conflicting results, with no clear superiority of one technique over the other[22-24]. A Cochrane review reported that there were insufficient data to recommend RFA over other thermal ablation techniques in the management of HCC[25], with the authors emphasising that only a single small RCT comparing MWA with RFA, with a total of 72 patients, had been performed[23]. Subsequently, a further six RCTs have been performed with the latest meta-analysis only including five RCTs and 21 cohort studies[26]. In this context, additional evidence, particularly from a comprehensive meta-analysis that incorporated all RCTs, and data from large real-world observational cohort studies would provide clinicians with a better understanding of whether the comparative overall efficacy and safety of MWA over RFA supports the current preferential use of MWA for the treatment of early-stage HCC.

This study was a contemporary systematic review and meta-analysis of RCTs and cohort studies to determine whether MWA is equivalent to or more effective than RFA in relation to the primary treatment endpoints of complete ablation (CA), local recurrence rate (LRR), local recurrence-free survival (LRFS), OS, and safety including adverse events.

MATERIALS AND METHODS

Literature search

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[27] were followed and the Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool[28] was used to perform this study. A systematic electronic search was conducted independently by two authors in the Ovid Medline, Embase, PubMed, Reference Citation Analysis, Cochrane library databases, and Web of Science was performed from the inception of each until the first week of October 2021 inclusive of the database of articles that were accepted but not yet published, as well as the clinical-trials.gov website to identify relevant articles for our review (Supplementary Tables 1–5). The search strategy used the search terms "radiofrequency ablation", "microwave ablation" and "hepatocellular carcinoma" both as exploded medical subject headings where possible, and as text words. In addition, reference lists of relevant articles including recent reviews, and systematic reviews related to locoregional therapy of HCC were searched. Studies were limited to cohort studies and RCTs using appropriate hedges for each database. A search for unpublished literature was also performed.

Eligibility criteria

Studies were included using the following criteria: (1) Patient age ≥ 18 years; (2) diagnosis of HCC by American Association for the Study of Liver Disease imaging criteria[29] or histopathology; (3) HCC of any size; and (4) no evidence of macrovascular invasion or extrahepatic spread. Studies were excluded based on the following criteria: (1) Case series; (2) studies from the same group that contain overlapping patient populations; (3) treatment with any other modality in conjunction with local ablation therapy with microwave ablation or radiofrequency ablation; (4) non-HCC liver cancer; and (5) Studies where treatment was given as a bridge to liver transplantation.

Study outcomes

The primary outcomes of this study were CA, LRR, LRFS, OS and safety including adverse events and complications. CA was defined in studies as the absence of residual HCC on follow-up imaging postablation. LRR was defined in studies as the development of HCC lesions within the same liver segment as the treated tumour on imaging after CA. LRFS was defined as the proportion of patients alive at various timepoints in the absence of any evidence of local recurrence of HCC after treatment. Included studies had to have reported at least one of the primary endpoints as part of an RCT or observational cohort study.

Selection process

The initial literature search was performed independently by two reviewers (MJT and JL) to identify relevant articles based on the above inclusion and exclusion criteria. Where a difference of opinion occurred on the inclusion of studies for the review, consensus agreement was obtained *via* formal discussion between the two reviewers.

Data collection and bias assessment

Included RCTs were assessed for methodological quality and were classified as being of low, high, or unclear risk of bias according to the Jadad scale[30]. Included cohort studies were quality assessed using the Newcastle–Ottawa Scale[31] where a value ≥ 7 qualified the study as high quality. Data were extracted from the selected studies independently using a data extraction form to collect data on the following: (1) Study details (first author, publication year, journal, country, study design, interventions used, intervention group size); (2) baseline participant characteristics (age, sex, and cirrhosis status); (3) tumour characteristics (tumour stage and staging system, largest nodule size, nodule number, alfa-fetoprotein level, mean-tumour size); (4) intervention details; and (5) outcome measures: (complete ablation, local recurrence rate, overall and local recurrence free survival, adverse events, 30-d mortality).

Statistical analysis

A random-effects model using the method of DerSimonian and Laird was used for each outcome. Meta-regression analysis was performed to adjust for the difference in follow-up period between the studies.

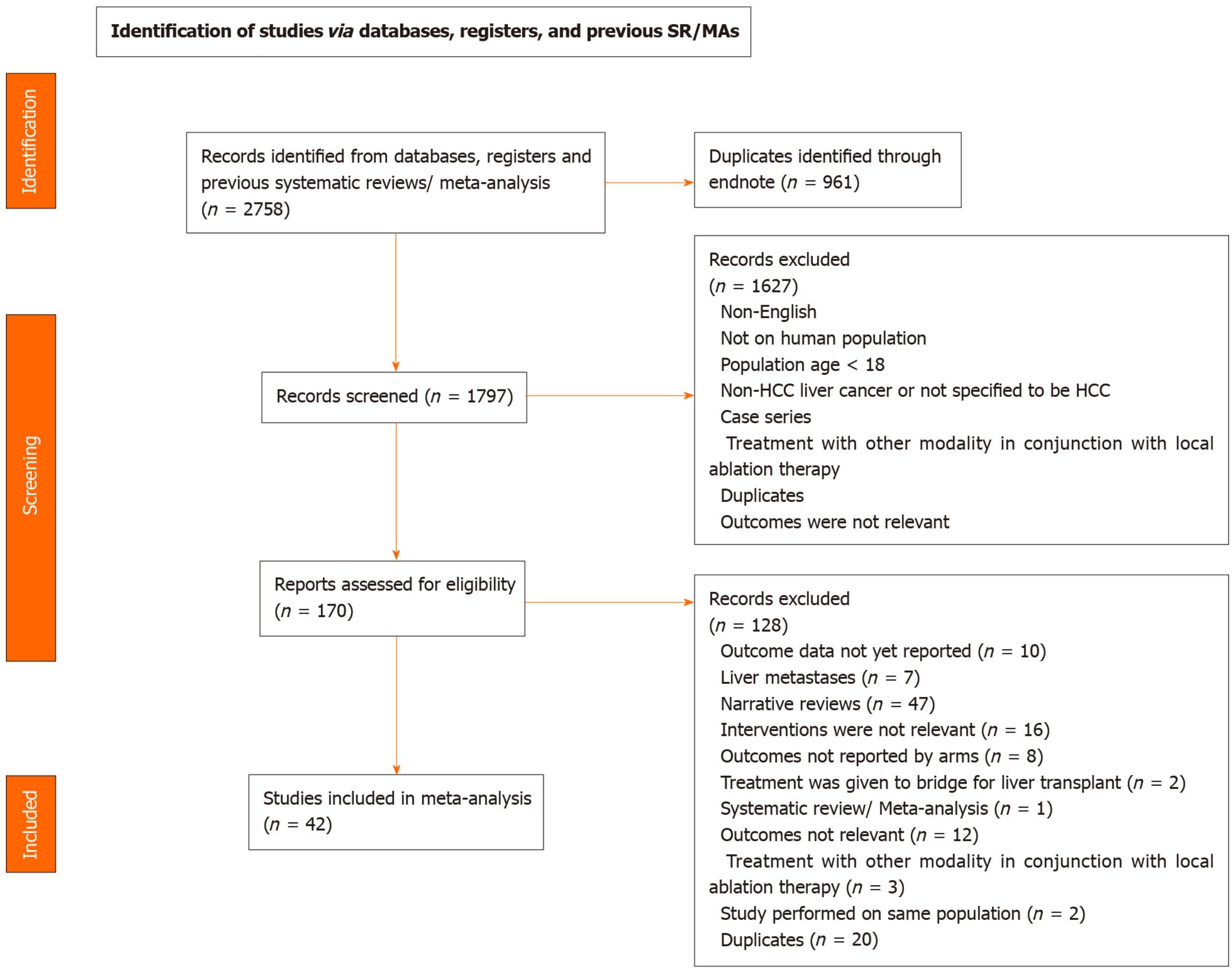

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Figure 1 Flowchart of search strategy and article screening process.

Analysis was also performed individually for RCTs, prospective and retrospective cohort studies. Heterogeneity was assessed using the I^2 statistic with results of 30%–60% (moderate), and > 50% (high) levels of heterogeneity[32]. Outcomes were reported using a pooled odds ratio (OR) and hazard ratio (HR) with 95% confidence interval (CI). We assessed publication bias using the Egger's regression model only if there were > 10 studies. All analyses were performed with Comprehensive Meta-analysis (version 3.0), Biostat, Englewood, NJ (2014). The statistical methods of this study were reviewed by academic statistician Guy Eslick from Clued Ptd Ltd.

RESULTS

Study selection and characteristics of included studies

As shown in Figure 1, the search strategy utilised for this meta-analysis identified 2758 studies initially. After removing duplicates and excluding studies based on our inclusion and exclusion criteria, 170 studies were assessed for eligibility from which a total of 42 studies, eight RCTs[22,23,33-38] and 34 cohort studies[33,39-71] were finally included in the meta-analysis. The main characteristics of included studies are reported in Table 1. The sample size of included studies (eight RCTs and 34 cohort studies) ranged from 42 to 879, with males forming the majority. In total, we examined a cohort of 6719 patients. A total of 24 studies were conducted in Asia, nine in Europe, five in Egypt, two in the USA, and one each in Australia and Turkey. Study follow-up duration ranged from 3 to 126 mo and was performed through the utilisation of computed tomography or magnetic resonance imaging. Across all studies, the mean age reported was 61 years. Most studies recruited patients with Child–Pugh stage A and B liver disease with only one RCT and nine cohort studies recruiting stage C patients. Notably, all 42 studies were comparable with regards to clinical and tumoral parameters. Maximum nodule sized ranged from 9 to 55 mm in RCTs and 8 to 60 mm in cohort studies. In total, six RCTs and 18 cohort studies reported mean tumour size. There was no significant difference in tumour size treated with MWA compared to

Table 1 Summary of patient characteristics of included randomised controlled trials and cohort studies

Ref.	Design	Country	Year	Arms	NP	Age/yr	% males	NL	Tumour size, mean or median (range or SD)/mm	CPC (A/B/C)	F/U Duration/mo
Abdelaziz *et al* [72], 2014	RCT	Egypt	2009-2011	MWA	66	53.6 (48.6-58.6)	72.7	76	29 (19.3-38.7)	25/41/0	NR
				RFA	45	56.8 (49.5-64.1)	68.9	52	29.5 (19.2-39.8)	24/21/0	
Chong *et al*[34], 2020	RCT	Hong Kong	2011-2017	MWA	47	63 (50–80)	63.8	NR	31 (20–45)	39/7/1	38.3 (2.3–78.0)
				RFA	46	64.5 (42–5)	82.6		28 (20–55)	40/6/0	33.9 (4.9–72.7)
Kamal *et al*[35], 2019	RCT	Egypt	2017	MWA	28	55 (42-80)	75	34	32.5 (23.3-41.7)	22/6/0	12
				RFA	28	55 (42-80)	78.6	34	32.8 (23.7-41.9)	22/6/0	12
Qian *et al*[36], 2012	RCT	China	2009-2010	MWA	22	52 (43–75)	90.9	22	21 (17-25)	22/0/0	5.1 ± 1.3 (2.8-6.5)
				RFA	20	56 (43–76)	95	20	20 (15-25)	20/0/0	5.1 ± 1.3 (2.8-6.5)
Shibata *et al*[23], 2002	RCT	Japan	1999-2000	MWA	36	62.5 (52–74)	66.7	46	22 (9–34)	19/17/0	18 (6-27)
				RFA	36	63.6 (44–83)	72.7	48	23 (10–37)	21/15/0	18 (6-27)
Tian *et al*[37], 2014	RCT	China	2014	MWA	120	NR	NR	86	26 (13-39)	NR	NR
				RFA				79	22 (13-31)		
Vietti *et al*[38], 2018	RCT	France & Switzerland	2011-2015	MWA	76	NR	NR	98	NR	NR	26 (18-29)
				RFA	76			104			25 (18-34)
Yu *et al*[22], 2017	RCT	China	2008-2015	MWA	203	NR	NR	265	27 (7– 50)	NR	35.2 (2.0–81.9)
				RFA	200			251	26 (9–50)		35.2 (2.0–81.9)
Abdel-Samiee *et al*[33], 2020	Retro	Egypt	2020	MWA	50	NR	NR	NR	NR	NR	36
				RFA	50						36
Bouda *et al*[39], 2020	Retro	France	2008-2016	MWA	79	62.8 (52.4-73.2)	81	99	21.3 (13-29.6)	71/8/0	34 (3–65)
				RFA	43	62.2 (50.3-74.1)	76.7	52	23.0 (14.9-31.1)	39/4/0	40 (5–126)
Chinnaratha *et al* [40], 2014	Retro	Australia	2006-2012	MWA	101	62.1 (51.7-72.5)	98	NR	21.1 (10.9-31.3)	92/23/2	36
				RFA	25	62.1 (51.7-72.5)	98		21.1 (10.9-31.3)		36
Cillo *et al*[41], 2014	Pros/Retro	Italy	2004-2010	MWA	42	64 (47–81)	83	50	NR		24
				RFA	100	63 (34–81)	83	NR			24
Ciruolo *et al*[42], 2020	Retro	Italy	2013-2019	MWA	NR	64	71.7	78	NR	NR	NR
				RFA				172			

Ding *et al*[43], 2013	Retro	China	2006-2010	MWA	113	59.06 (30–86)	75.2	131	25.5 (8–50)	75/38/0	18.3 (3–51.4)
				RFA	85	58.64 (40–77)	80	98	23.8 (10–48)	49/36/0	27.7 (4–60)
Du *et al*[44], 2020	Retro	China	2014-2016	MWA	218	56.3 (46.3-66.3)	80	136	24 (13-35)	107/8/0	28 (15-51)
				RFA	234	57.5 (48-67)	76.5	137	26 (15-37)	105/10/0	
Gaia *et al*[45], 2021	Retro	Italy	2013-2019	MWA	81	67 (57–73)	76.5	77	29 (20–35)	71/10/0	20.4 (10.8-38.4)
				RFA	170	63 (56–72)	69.4	169	20 (15–25)	148/22/0	34.8 (19.2–51.6)
Ghweil *et al*[46], 2019	Pros	Egypt	2019	MWA	25	NR	NR	NR	NR	NR	NR
				RFA	30						
Iida *et al*[47], 2013	Retro	Japan	2001-2012	MWA	40	70.1 (63.5-76.7)	NR	NR	20 (11-29)	NR	NR
				RFA	18	73.5 (69.5-77.5)			21 (16-26)		
Ding *et al*[48], 2013	Retro	China	2002-2011	MWA	556	58.4 (48.1-68.7)	74.8	1090	23 (12-34)	466/167/22	(6-75)
				RFA	323	58 (47.8-68.3)	79.8	562	22.8 (11.7-33.9)	248/106/22	(6-75)
Kuang *et al*[49], 2011	Pros	China	1997-2008	MWA	19	55 (27-74)	94	NR	NR	77/4 /0	45 (24-155)
				RFA	31						
Kumbar *et al*[50], 2018	Retro	India	2018	MWA	25	(40-85)	92	33	NR	13/8/4	15
				RFA	25		88	35		17/8/0	
Lee *et al*[51], 2017	Retro	Hong Kong	2003-2011	MWA	26	62.5 (49-79)	73.1	28	37.5 (20-60)	23/3/0	47.5 (11.3-62.5)
				RFA	47	58 (43-77)	85.1	52	31 (20-60)	42/5/0	52.9 (3.6-121.8)
Liu *et al*[52], 2018	Retro	China	2002-2017	MWA	126	54 (45, 60)	90.5	162	22.5 (17, 29)	NR	36.8 (1-115)
				RFA	436	56 (46, 65)	89.7	482	23.0 (18, 30)		34.1 (1-171)
Loriaud *et al*[53], 2018	Retro	France & Switzerland	2007-2015	MWA	NR	69 (61–75)	92.5	40	22.5 (10–47)	40/0/0	28 (10-46)
				RFA		67 (58-74)	85.8	120	21.3 (10-46)	111/9/0	
Lu *et al*[54], 2005	Retro	China	1997-2002	MWA	49	50.1 (24–74)	89.8	98	25 (9–72)	22/27/0	25.1 (2.0–50.6)
				RFA	53	54.5 (20–74)	81.1	72	26 (10–61)	47/6/0	24.8 (2.0–51.0)
Mocan *et al*[55], 2017	Retro	Romania	2010-2016	MWA	NR	NR	NR	22	NR	NR	12 (5.6-18.4)
				RFA				79			22.8 (7.8-37.4)
Nocerino *et al* [56], 2016	Retro	Italy	2016	MWA	106	NR	NR	134	20.4 (11-37)	NR	12 (5.6-18.4)
				RFA	27			35	20.1 (7-34)		22.8 (7.8-37.4)
Ohmoto *et al*[57], 2008	Retro	Japan	2002-2006	MWA	49	64 (38–75)	83.7	56	17 (8–20)	31/14/4	33.5 (9.8-57.2)

				RFA	34	67 (44–78)	73.5	37	16 (7–20)	20/11/3	25.9 (14.6-37.2)
Potretzke *et al* [58], 2016	Retro	US	2001-2013	MWA	99	61 (44–82)	81.8	136	22 (20–23)	NR	24
				RFA	55	62 (23–88)	72.7	69	24 (22–26)		31
Sakaguchi *et al* [59], 2009	Pros	Japan	2009	MWA	142	NR	NR	NR	NR	NR	NR
				RFA	249						
Santambrogio *et al*[60], 2017	Retro	Italy	2009-2015	MWA	60	70 (61.7-78.3)	72	NR	21.5 (16.2-26.8)	60/0/0	31 (15–46)
				RFA	94	69 (60-78)	73		19.2 (14.2-24.2)	94/0/0	
Sever *et al*[61], 2018	Retro	Turkey	2012-2015	MWA	20	63.6 (57.3-69.9)	65	37	28 (18-38)	14/4/2	12 (1-40)
				RFA	20	64.3 (55.3-73.3)	70	34	24 (13-35)	11/4/5	
Shum *et al*[62], 2016	Retro	Hong Kong	2014-2015	MWA	22	NR	NR	NR	NR	NR	19
				RFA	44						18
Simo *et al*[63], 2011	Retro	US	2006-2008	MWA	13	59.6 (49–72)	54	15	23.1 (14–39)	12/7/3	7 (2.5–10.5)
				RFA	22	58 (45–79)	86	27	25.3 (12–44)	7/6/0	19 (1.5–31)
Suwa *et al*[64], 2021	Retro	Japan	2014-2020	MWA	72	74.9 (66.5-83.3)	65.3	NR	17.7 (10.9-24.5)	58/14/0	12
				RFA	72	74.4 (65.2-83.6)	68.1	NR	17.6 (11.3-23.9)	61/11/0	37.8
Suwa *et al*[65], 2020	Retro	Japan	2016-2019	MWA	44	73.4 (65.7-81.1)	68	52	17.2 (12.3-22.1)	12/3/29	NR
				RFA	55	73.4 (65.7-81.1)	80	70	17.7 (11.3-24.1)	16/8/31	
Vogl *et al*[66], 2015	Retro	Egypt	2008-2010	MWA	28	60 (45-68)	82.1	32	36 (9-50)	NR	NR
				RFA	25	57 (40-64)	76	36	32 (8-45)		
Xu *et al*[67], 2004	Retro	China	1997-2001	MWA	54	53.4 (24–74)	86.6	112	25 (15-36)	53/33/11	27.4 (2–53)
				RFA	43			78	26 (12-40)		
Xu *et al*[68], 2017	Retro	China	2007-2012	MWA	301	54.2 (43.2-65.2)	78.1	NR	17 (14-20)	278/23/0	53 (8–98)
				RFA	159	54.0 (43-65)	83		17 (14-20)	140/19/0	62 (6–102)
Yin *et al*[69], 2009	Retro	China	1997-2007	MWA	49	53 (41-65)	87.2	NR	39 (31-47)	NR	22 (2.2-93.5)
				RFA	59						
Zhang *et al*[70], 2013	Retro	China	2006	MWA	77	54 (26–76)	70.2	105	NR	77/0/0	24.5 (6–64)
				RFA	78	54 (30–80)	82.1	93		78/0/0	26.3 (7–65.6)
Zhang *et al*[71], 2014	Pros	China	2014	MWA	45	NR	NR	60	NR	NR	NR

RFA	56	68

CPC: Child Pugh Score; MWA: Microwave ablation; NP: Number of patients; NL: Number of lesions, NR: Not reported; RFA: Radiofrequency ablation.

RFA in both RCTs (OR 1.13, 95%CI 0.88–1.46) and cohort studies (OR 0.96, 95%CI 0.77–1.20) (Supplementary Figure 1). Furthermore, there was no significant difference in mean tumour size amongst RCTs (OR 0.05, 95%CI -0.07 to 0.18; P = 0.395) and cohort studies (OR -0.01, 95%CI -0.09 to 0.07; P = 0.777) (Supplementary Figure 2). The total number of lesions treated per study with MWA and RFA ranged from 15 to 1090 and 20 to 562, respectively.

Quality assessment

Seven of the eight RCTs assessed were deemed to be high quality with one study[22] deemed to be of low quality (Supplementary Table 6). All RCTs were determined to be at high risk of performance bias as it was not practical to blind the administrator to the procedure. However, four RCTs[23,34,37,38] were able to blind the outcome of assessment. Potential for selection and detection bias was identified in four RCTs[22,35,36,72]. Of the 34 cohort studies identified, 30 scored a value of 7 or higher, meeting the definition of a high-quality study (Supplementary Table 7).

CA

Seven RCTs[22,23,34-37,72] and 24 cohort studies[39,42-46,48-51,54,55,60-71] reported data on CA post-treatment. No significant difference in the CA rate was found between the MWA and RFA groups in the prospective cohort studies (OR 0.95, 95%CI 0.28–3.23; P = 0.82)[41,46,49,59,71] and RCTs (OR 1.18, 95%CI 0.64–2.18; P = 0.60)[22,23,34-37,72]. However, retrospective cohort studies reported higher CA rates with MWA compared to RFA (OR 1.29, 95%CI 1.06–1.57; P = 0.01) (Figure 2A)[39,42-45,48,50,51,54,55,60-70]. No evidence of heterogeneity was found in these studies (P = 0.99). Funnel plot analysis concluded that publication bias was unlikely (Figure 2B).

OS

Five RCTs[22,34,35,38,72] and 17 cohort studies[33,41,43,47,51,52,54,57,59-63,66,68,70,71] reported data on OS post-ablation (Table 2). Heterogeneity was identified in the results reported at 3 and 4 years by retrospective cohort studies (Table 2)[33,43,51,52,54,57,66,68,70]. In studies that categorised data into OS into specific years, no significant difference in OS was noted between MWA and RFA groups. Meta-analysis of four retrospective studies that did not specify the follow-up period[52,54,59,63] reported significantly higher OS in patients treated with MWA. No potential bias was identified during visual assessment and Egger's test of funnel plot.

Individual study OS rates were plotted on a dot graph for both MWA and RFA treated subjects (Figure 3) with median OS rates according to year of follow-up post-treatment shown in Table 3. Of note, MWA was associated with improved median OS at 3 and 4 years of follow-up but this difference was lost at 5 years.

LRR

Six RCTs[22,23,35,36,38,72] and 26 cohort studies[39-41,43,44,46,47,49,51-58,60,61,63-70] reported data regarding LRR following ablation (Table 2). One RCT[22] reported lower 5-year LRR when patients were treated with MWA (OR 0.52, 95%CI 0.30–0.91; P = 0.023). Heterogeneity was identified in the results reported at 1, 2 and 3 years by retrospective cohort studies while meta-analysis of two retrospective cohort studies[53,57] reported a higher 4-year LRR in patients treated with MWA (OR 2.14, 95%CI 1.12–4.07, P = 0.021) (Table 2). However, meta-analysis of 20 retrospective cohort studies that reported LRR over an unspecified period[39-41,43,44,46,52-54,56-58,60,63,65-70] concluded that LRR was significantly lower in patients treated with MWA (OR 0.67, 95%CI 0.51–0.87, P = 0.002). Three cohort studies reported LRR according to tumour size ≤ 3 cm[43,52,54] with no statistcally significant differences identified between the MWA and RFA groups (OR 0.86, 95%CI 0.45–1.64, P = 0.64). No potential bias was identified during visual assessment and Egger's test of funnel plot.

HR for OS and LRR

Four RCTs[22,34,38,72] and 18 cohort studies[39,41,43-45,51-53,57-61,64,66,68,70] reported HR data regarding OS (Table 4). No significant differences were noted in OS between both arms. However, there was a trend towards better OS rates in patients treated with MWA in both RCTs (P = 0.08) and prospective cohort studies (P = 0.08) over an unspecified period (Table 4). Five retrospective cohort studies reported HR data regarding LRR[39,53,58,61,64]. No significant differences were noted in LRR between both arms. No potential bias was identified during visual assessment and Egger's test of funnel plot.

Table 2 Summary of the comparison of OS and local recurrence rates between microwave ablation *versus* radiofrequency ablation for intrahepatic hepatocellular lesions in both cohort studies and RCTs according to year of follow-up

Endpoint	Study design	No. of studies	OR	95%CI	*P* for significance	I^2	*P* for heterogeneity
Overall survival – OR							
1Y	Prospective	1	3.00	0.33-27.48	0.331	-	-
	Retrospective	11	1.19	0.71-1.99	0.513	0	0.72
	RCT	4	1.95	0.71-5.34	0.194	35.5	0.20
2Y	Retrospective	7	1.27	0.75-2.18	0.377	36.6	0.15
	RCT	1	1.84	0.54-6.28	0.333	-	-
3Y	Prospective	1	1.69	0.59-4.81	0.328	-	-
	Retrospective	9	1.14	0.75-1.73	0.554	58.1	0.01
	RCT	2	0.98	0.62-1.54	0.929	0	0.62
4Y	Retrospective	5	0.77	0.46-1.29	0.323	60.8	0.04
5Y	Prospective	2	1.49	0.31-7.22	0.620	71.2	0.06
	Retrospective	5	0.86	0.62-1.19	0.357	34.8	0.19
	RCT	2	0.79	0.50-1.15	0.197	0	0.76
Unspecified	Retrospective	4	1.54	1.15-2.05	0.004	0	0.50
	RCT	2	1.47	0.73-2.96	0.282	0	0.50
Local recurrence rate – OR							
1Y	Retrospective	4	0.78	0.29-2.11	0.619	62.8	0.04
	RCT	3	1.09	0.39-3.05	0.872	0	0.40
2Y	Retrospective	4	1.00	0.40-2.45	0.992	76.2	0.06
	RCT	2	1.02	0.23-4.58	0.975	70.4	0.07
3Y	Retrospective	2	0.80	0.11-5.97	0.826	84.8	0.01
	RCT	1	0.73	0.30-1.8	0.493	-	-
4Y	Retrospective	2	2.14	1.12-4.07	0.021	0	0.86
5Y	Prospective	1	2.22	0.49-10.02	0.301	-	-
	RCT	1	0.52	0.30-0.91	0.023	-	-
Unspecified	Prospective	3	0.60	0.25-1.39	0.233	0	0.44
	Retrospective	20	0.67	0.51-0.87	0.002	37.2	0.05
		1	0.26	0.06-1.07	0.063	-	-

OS: Overall survival; OR: Odds ratio; CI: Confidence interval; RCT: Randomised controlled trial.

LRFS

One RCT[35] reported that there was no significant difference between MWA and RFA with regards to 1-year LRFS (OR 1.175, 95%CI 0.178–7.737, *P* = 0.93). One cohort study[63] reported that there was no significant difference between MWA and RFA with regards to LRFS (OR 0.53, 95%CI 0.148–1.86).

Safety

Three RCTs[34,35,38] and 14 cohort studies[33,39,47,48,51,58,60,62-64,67-70] reported data regarding 30-d mortality (Figure 4). No significant differences were identified between the MWA and RFA groups in both RCTs (OR 1.00, 95%CI 0.19–5.14, *P* = 1.0) and cohort studies (OR 0.67, 95%CI 0.27–1.68, *P* = 0.39). There was no heterogeneity identified between studies. A sensitivity analysis excluding studies that reported no deaths in both arms was performed (Figure 4), but results remained consistent with the main analysis (OR 0.61, 95%CI 0.25–1.51, *P* = 0.29). No potential bias was identified during visual assessment and Egger’s test of funnel plot.

Table 3 Summary of the comparison of median and mean overall survival rates between microwave ablation *versus* radiofrequency ablation for intrahepatic hepatocellular carcinoma lesions in both cohort studies and randomised controlled trials

Year	MWA sample size	RFA sample size	Median OS		*P* value
			MWA	RFA	
1	1135	1623	96.2%	95.4%	0.31
2	651	789	90.7%	88.0%	0.10
3	1004	1480	80.5%	75.3%	0.002
4	421	464	76.8%	70.0%	0.02
5	764	1221	67.3%	69.5%	0.30

OS: Overall survival; MWA: Microwave ablation; RFA: Radiofrequency ablation.

Table 4 Summary of overall survival and local recurrence rate HRs

Endpoint	Study design	No. of studies	HR	95%CI	*P* for significance	I^2	*P* for heterogeneity
Overall survival – HR							
Univariate	Retrospective	2	1.17	0.75-1.83	0.497	17.5	0.27
Multivariate	Retrospective	3	1.32	0.92-1.89	0.130	0.8	0.36
Unspecified	Prospective	1	1.45	0.96-2.19	0.078	-	-
	Retrospective	13	1.06	0.86-1.32	0.580	58.6	0.004
	RCT	4	1.34	0.97-1.86	0.079	0	0.58
Local recurrence rate – HR							
Univariate	Retrospective	3	1.77	0.81-3.88	0.151	63.9	0.06
Multivariate	Retrospective	2	1.88	0.79-4.47	0.151	56.1	0.13
Cox proportional	Retrospective	1	2.17	1.04-4.50	0.040	-	-
Fine and gray	Retrospective	1	2.07	0.95-4.26	0.070	-	-
Unspecified	Retrospective	1	2.00	0.50-8.00	0.326	-	-

HR: Hazard ratio; CI: Confidence interval; RCT: Randomised controlled trial.

Table 5 Microwave ablation *versus* radiofrequency ablation for hepatocellular lesions: Meta-analysis of adverse events

Adverse event	No. of studies	OR	95%CI	*P* for significance	I^2	*P* for heterogeneity
Liver-related morbidity	11	1.51	0.64-3.55	0.342	0	0.91
Postprocedural infections	19	1.3	0.85-1.97	0.222	0	0.83
Postprocedural bleeding	10	2.36	0.92-6.07	0.075	0	0.97
Bile duct injury	5	1.88	0.57-6.23	0.299	0	0.99
Respiratory events	14	1.99	1.07-3.71	0.03	0	0.87
Local events	4	1.62	0.49-5.36	0.426	0	0.57

Liver related morbidity: Decompensation, jaundice, infarction, and portal vein thrombosis; Post-procedural infections: General, peritonitis, and liver abscess. Local events: Burns, pain, and wound complication; Respiratory events: Pleural effusion and pneumothorax. OR: Odds ratio; CI: Confidence interval.

With regard to morbidity, five RCTs[23,35,36,38,72] and 20 cohort studies[33,39,43,44,47-49,51,52,54,57,58,60,61,63-66,68,70] reported data on adverse events (Table 5). There were no significant differences in rates of liver-related morbidity, postprocedural bleeding and infections, local events, and bile duct injury when comparing the two interventions. MWA had a significantly increased rate of adverse

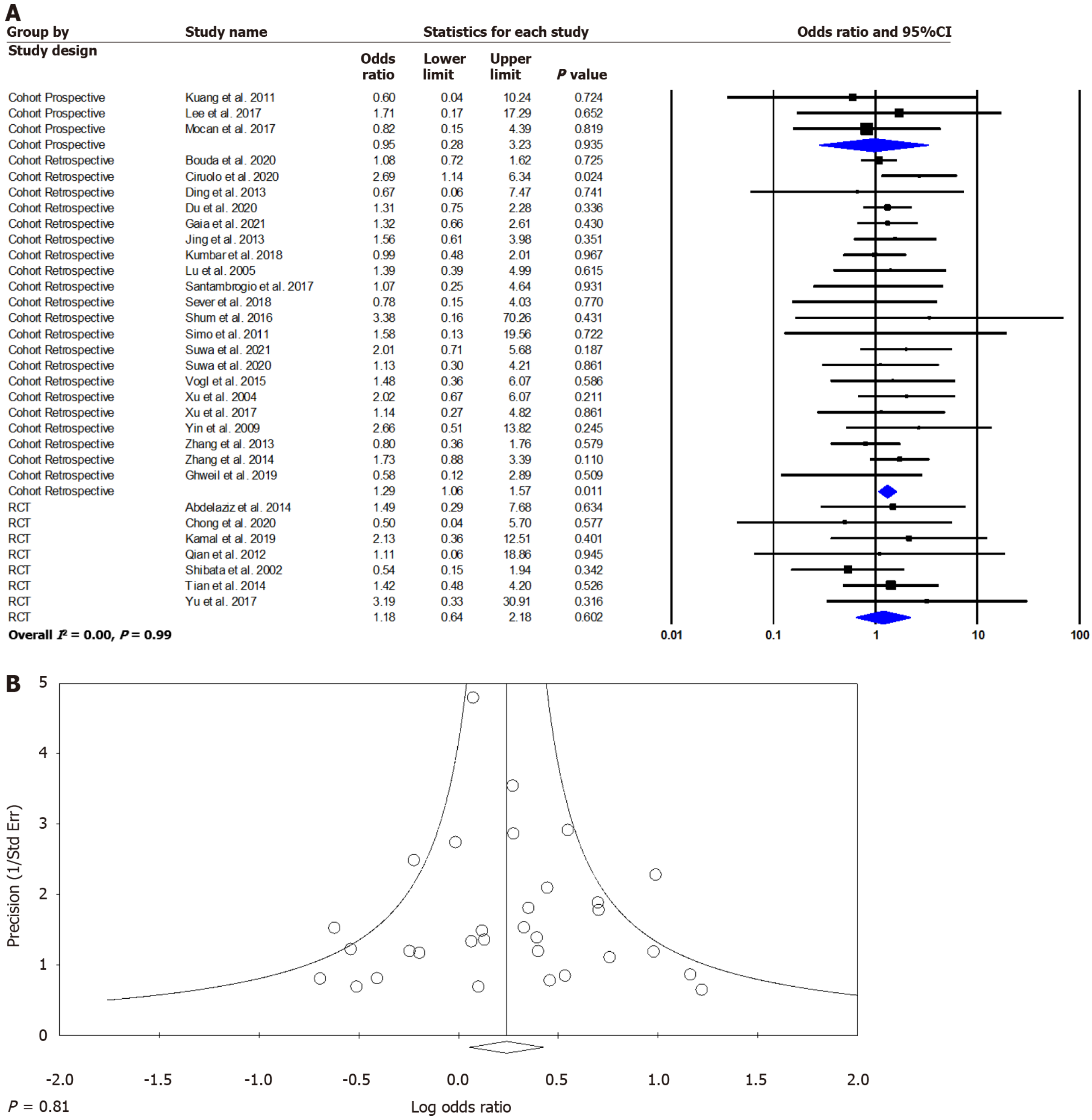

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Figure 2 Forest plot and funnel plot. A: Microwave ablation *versus* radiofrequency ablation for intrahepatic hepatocellular carcinoma lesions. Forest plot for complete ablation; B: Microwave ablation *versus* radiofrequency ablation for intrahepatic hepatocellular carcinoma lesions: Funnel plot for publication bias.

respiratory events when compared to RFA (OR 1.99, 95%CI 1.07–3.71, P = 0.03). No potential bias was identified during visual assessment and Egger's test of funnel plot.

DISCUSSION

Local thermal ablation is the standard of care for patients with unresectable early-stage HCC. MWA is increasingly preferred to RFA because of its ability to produce wider and more predictable ablation volumes over a shorter procedural time[17,19,22]. Moreover, MWA has theoretical advantages including minimising heat-sink effect that limits the use of RFA to lesions with proximity to adjacent structures. To our knowledge, our study is the most detailed systematic review and meta-analysis to date having identified 42 studies including eight RCT's and 34 cohort studies involving a total of 6719 subjects, that compared the outcomes of the two treatment modalities. Our main findings were that MWA achieves similar complete ablation rates compared with RFA, as well as lower LRR and similar OS. However, adverse events associated with MWA appear higher, particularly in relation to proc-

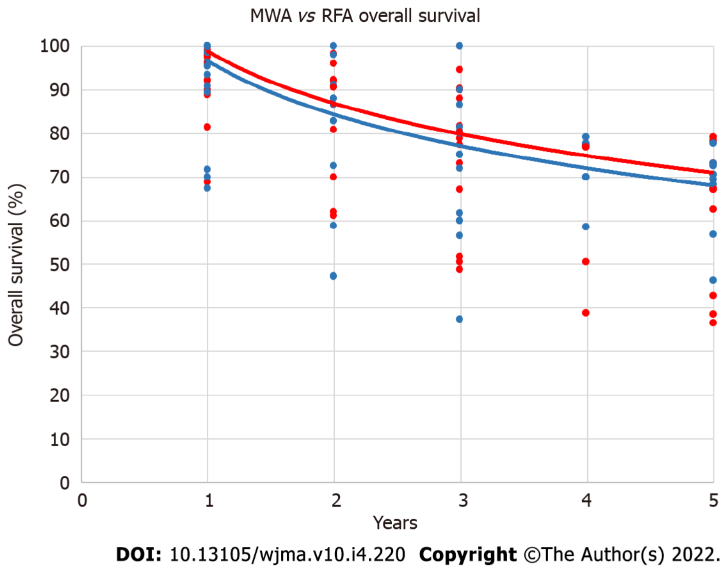

Figure 3 Dot plot of microwave ablation *versus* radiofrequency ablation overall survival rates over time. Trendlines are based on median survival. Microwave ablation is represented by red dots and red trendline while radiofrequency ablation is represented by blue dots and blue trendline. MWA: Microwave ablation; RFA: Radiofrequency ablation.

edure-related respiratory events.

In our study, we found MWA achieved similar or better CA rates than RFA depending on the study design. Notably CA rates were similar between the two modalities among RCTs, as previously reported [73,74], as well as among prospective cohort studies. However, higher CA rates were associated with MWA among retrospective cohort studies, which was likely due to multiple factors including patient selection, tumour size and the technique used; notwithstanding the fact that nearly threefold more cohort studies were captured in our study compared to other smaller meta-analyses of this type[24,40, 73]. These findings align with preclinical data that MWA results in higher intratumoral temperature and greater ablation range[75], that should in theory lead to faster ablation times and high rates of CA[76].

In addition, we identified MWA utilisation was overall associated with similar rates of local recurrence to RFA among RCTs and prospective cohort studies. However lower recurrence rates with MWA were reported among retrospective cohort studies, although results were inconsistent with two retrospective cohort studies reporting lower rates of local recurrence with RFA at the 4-year mark, while one RCT reported lower rates of LRR with MWA at the 5-year mark[22,53,54]. Moreover, because this was an analysis of LRR data without a specific timeframe, caution should be exercised as the follow-up for individual studies varied. Potential reasons for discordance in results include the fact that different generators were among studies as well as variation in the reporting outcomes with some studies reporting cumulative LRR. Notably, previous meta-analyses evaluating MWA and LRR have also drawn different conclusions, with two reports concluding that MWA resulted in significantly lower LRR [73,77], while a more recent study found no difference between both interventions[74]. These data combined with ours point to the fact that LRRs following MWA of HCC are at least as good as that following RFA.

An important finding from our study was the identification that MWA appears to lead to better OS, particularly among retrospective cohort studies. However, because this was mainly among studies with no specified follow-up period, we were unable to determine the timeframe to which the improvement in OS applies. Still, median OS rates tend to favour MWA particularly within the first few years postablation. Previous meta-analyses found that up until the 5-year mark, there was no difference between OS rates[24,40,73,74,77]. Except for Huo and colleagues[24]], these meta-analysis did not look at yearly OS. Long-term OS could be affected by interventional factors such as frequency, duration, and power of the ablative machines used. Furthermore, patient factors such as age, pre-existing liver disease and severity, and socioeconomic status could all contribute to OS. As we were unable to account for all these potentially confounding factors, it raises the question whether our results can be applied to the clinical setting with certainty.

In relation to adverse events, previous meta-analyses have concluded that there was no difference in complication rates between both interventions[24,73,74]. In our study, we identified a significantly increased rate of adverse respiratory events (*i.e.*, pleural effusion and pneumothorax) associated with MWA in 14 studies but no significant differences in local and/or liver related complications. This novel finding could influence the current perception that MWA has a similar safety profile to that of RFA despite the larger ablation zone. One possible explanation of the presence of pleural effusions could be due to thermal injury to the diaphragm resulting in an inflammatory response and/or diaphragmatic

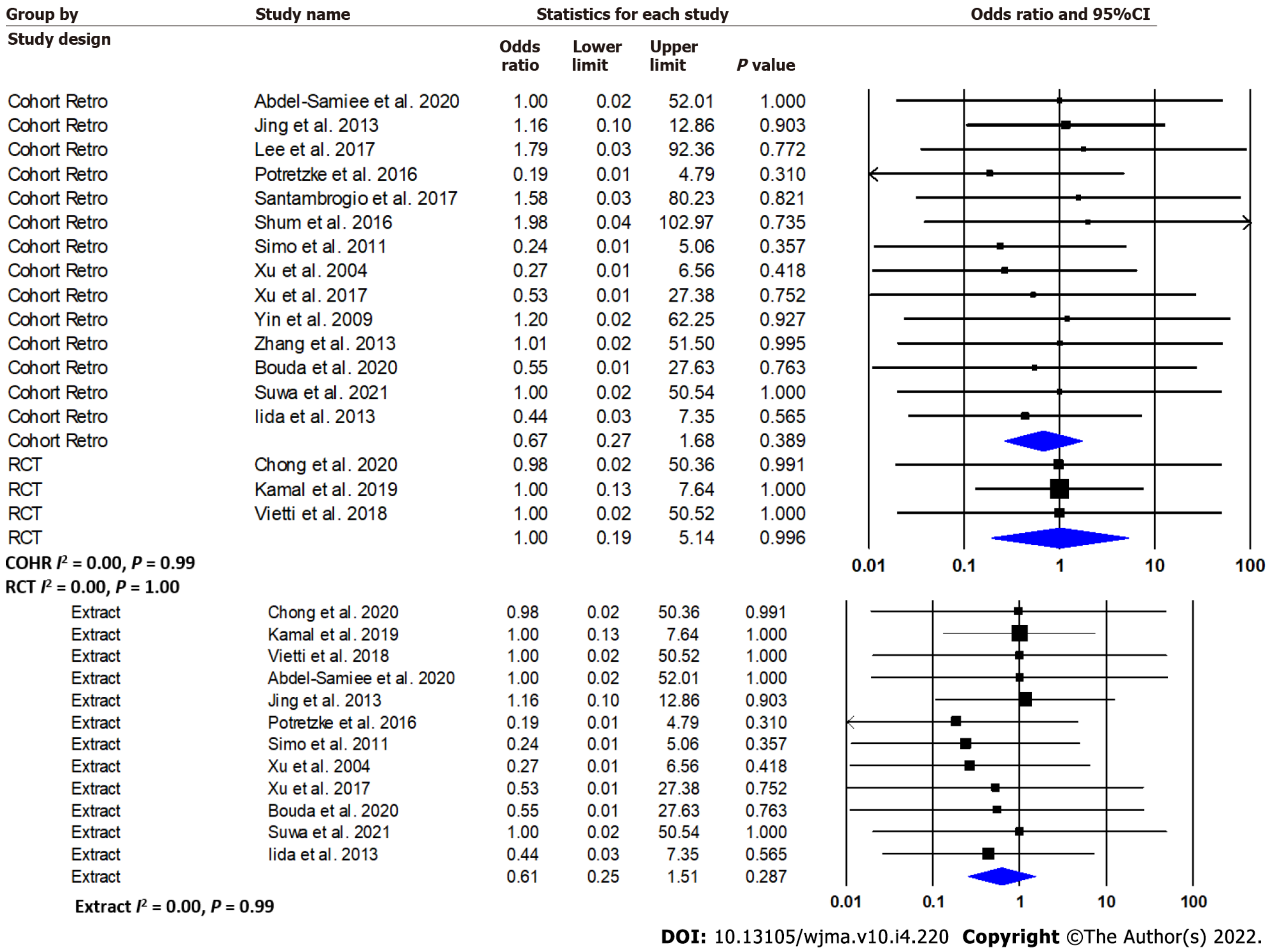

Figure 4 Microwave ablation *versus* radiofrequency ablation for intrahepatic hepatocellular carcinoma lesions: Forest plot for 30-d mortality.

microperforations resulting in leakage of fluid from the peritoneal cavity to the pleural space. Similarly, the increased rates of pneumothorax could reflect inadvertent pleural puncture with subsequent air leakage into the pleural space. Ultimately, this novel safety finding adds a layer of complexity when making the decision to choose between MWA or RFA for ablating HCC.

The strengths of our study included it being, to our knowledge, the most comprehensive study on this topic to date. We examined a large cohort of 6719 patients that enabled us to identify outliers and provide results with a smaller margin of error. In addition, data were categorised based on follow-up period, allowing us to identify if the difference between our primary outcomes for each individual year was significant. Finally, an analysis of tumour size was performed ruling out a potential confounding factor. Nevertheless, our findings should be interpreted with caution in view of certain limitations. Firstly, only studies published in English were included, which could lead to selection bias. Secondly, we did not explore the influence of generators and antennas used to perform the procedures which could present as a confounding factor. Furthermore, although we had a significant number of RCTs, the majority of studies were retrospective cohort studies that are susceptible to both selection bias and information bias due to the difficulty in achieving accurate record keeping and recounts of events, as well as complete data retrieval. Conference abstracts were included in our study which allowed for a more comprehensive look at the subject matter but potentially at the cost of preliminary results. Also, a significant number of studies included were conducted by a single centre, and hence subject to patient selection bias. Moreover, eligibility criteria for inclusion of patients were not standardized among studies.

CONCLUSION

Our results suggest that compared to RFA, MWA achieves similar CA rates and as good or better longer-term outcomes in relation to LRR and OS. Our analysis of tumour size suggests that it is unlikely to affect our conclusion. Apart from an increased likelihood of postprocedural respiratory events, MWA is as safe as RFA. Current guidelines recommend RFA to bridge transplantation or in early HCC[10,78].

Our novel results suggest that all guidelines should consider these ablative techniques as being interchangeable as standard of care.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is the seventh most common cancer and second leading cause of cancer mortality. Of the common modalities used to ablate HCC, radiofrequency ablation (RFA) is the most strongly recommended. Recently, microwave ablation (MWA) has become a popular ablative technique because of its reduction in heat-sink effect, ability to produce wider and more predictable ablation volumes.

Research motivation

Studies to date comparing outcomes of MWA with RFA have yielded conflicting results, with no clear superiority of one technique over the other. In this context, additional evidence particularly from a comprehensive meta-analysis that incorporate all RCTs and data from large real-world observational cohort studies would provide clinicians with a better understanding.

Research objectives

This study was a contemporary systematic review and meta-analysis of RCTs and cohort studies to determine whether MWA is equivalent to or more effective than RFA in relation to the primary treatment endpoints of complete ablation (CA), local recurrence rate (LRR), local recurrence-free survival, overall survival (OS), and safety including adverse events.

Research methods

A systematic electronic search was conducted independently by two authors. Quality of included studies were assessed using the Jadad scale for RCTs and Newcastle–Ottawa Scale for cohort studies. A random-effects model using the method of DerSimonian and Laird was used for each outcome. Meta-regression analysis was performed to adjust for the difference in follow-up period between the studies.

Research results

A total of 42 studies, eight RCTs and 34 cohort studies were included in the meta-analysis, allowing us to examine a total cohort of 6719 patients. CA rates between MWA and RFA groups were similar in prospective cohort and RCTs; however, retrospective studies reported higher rates with MWA. Retrospective cohort studies reported higher OS and lower LRR. MWA had an increased rate of adverse respiratory events when compared to RFA.

Research conclusions

MWA achieves similar CA rates and as good or better longer-term outcomes in relation to LRR and OS compared to RFA. Apart from an increased rate of respiratory events post procedure, MWA is as safe as RFA.

Research perspectives

Current literature on local recurrence free survival is lacking and has potential to be explored in future studies.

FOOTNOTES

Author contributions: Tang MJ performed the systematic review, acquisition and interpretation of the data, drafting the article, and final approval; Eslick GD performed the statistical analysis and interpretation of the data, drafting the article, and final approval; Lubel JS performed the systematic review, acquisition and interpretation of the data, drafting the article, and final approval; Majeed A performed interpretation of the data, review of the article, and final approval; Majumdar A contributed to the study design, interpretation of the data, review of the article, and final approval; Kemp W contributed to study concept and design, interpretation of the data, drafting and review of the article, and final approval; Roberts SK contributed to study concept and design, interpretation of the data, drafting and review of the article, and final approval.

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