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Identifying risk factors for mortality in patients admitted to hospital with COVID-19

An evidence summary based on the following systematic review: Tian, W, Jiang, W, Yao, J, et al. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. *J Med Virol.* 2020; 92: 1875– 1883. <https://doi.org/10.1002/jmv.26050>

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Introduction

There have been 112,456,453 confirmed cases of Covid-19 worldwide resulting in 2,497,514 deaths (February 26, 2021)⁽¹⁾. As a relatively new disease, little is known about the clinical predictors of COVID-19 specific mortality⁽²⁾. Previous reviews have focused on either severity of the disease^(3,4) or specific comorbidities^(5,6) linked to mortality, where in many cases the evidence has been limited. Subsequently, the systematic review by Tian et al. aims to re-evaluate the current body of evidence to comprehensively clarify predictors of mortality in hospitalised patients with COVID-19⁽²⁾. This commentary aims to critically appraise the methods used within this systematic review and meta-analysis to discuss the findings in the context of current clinical practice.

Methods

A multi-database search was undertaken from January 1, 2020 to April 24, 2020 with no language restrictions. Additional searches of systematic reviews and eligible studies' citation lists were screened for eligible articles. No clear criteria were set for the population under examination based on the aims of the review. The patients needed to be hospitalised and have COVID-19 but there was no clear indication of how this was defined. Family-based studies and those which reported paediatric only cases were excluded, as were those which did not clearly report death as an outcome. Screening, data extraction and quality assessment (Agency for Healthcare Research and Quality (AHRQ)) were carried out by two independent reviewers. A random effects meta-analysis was undertaken to compare a range of clinical features clustered around comorbidities, clinical manifestations, and gender.

Results

Fourteen cross-sectional studies comprising of 4659 hospital patients were included in the systematic review. Thirteen of the studies were conducted in China (2025 patients) and one large study in New York (2634 patients). There were 2681 male participants (57.5%) and the mean age was 59.8. Significant comorbidities reported across all patients were hypertension (43.6%), diabetes (23.8%) and coronary heart disease(CHD)/cardiovascular disease (12.4%). The most prevalent clinical symptoms reported across all patients were: fever (88%), fatigue (44.5%) and myalgia (21.1%). The mortality rate for hospitalised COVID-19 patients was 25.5% (1189 patients) with a higher risk for males (odds ratio [OR] 1.8; 95%CI 1.3-2.4, $p=0.0003$) and older patients (mean difference [MD] 15.6%; 95%CI 12.5-18.6, $p<0.00001$).

Fatigue was the only clinical symptom that had a clear association with mortality (OR 1.6; 95%CI 1.1-2.5, $p=0.03$). A statistically significant higher risk of mortality was identified for COVID-19 patients presenting with the following comorbidities: hypertension (OR 2.5; 95%CI 2.1-3.1; $p<0.00001$), diabetes (OR 2.0; 95%CI, 1.7-2.3; $p<0.00001$), CHD/cardiovascular disease (OR 3.8; 95%CI 2.1-6.9,

$p < 0.00001$), cerebrovascular disease (OR 4.9; 95%CI 1.5-15.7, $p = 0.007$) and chronic renal disease (OR 9.4; 95%CI 3.2-27.4, $p < 0.0001$). Of these, the most prevalent amongst patients who died were hypertension (56.8%), diabetes (31.2%) and CHD/cardiovascular disease (21.5%). No significant association was found between COPD or smoking and death although these were only reported in 4 studies.

Multiple disease biomarkers were statistically higher on admission for the non-survivor group compared to those who survived. These included markers for myocardial injury (cardiac troponin), heart failure (NT-proBNP), inflammatory processes, (interleukin-6, C-reactive protein, erythrocyte sedimentation rate) and liver/renal function (bilirubin, alanine transaminase, aspartate transaminase, creatinine, blood urea nitrogen and lower albumin). A higher rate of procalcitonin (a marker for sepsis), was also identified in the non-survivor group. There was a significantly greater risk of coagulopathy in the non-survivor group (lower platelet count) and the D-dimer measurements were higher. Biomarkers for immune cell counts also differed between survivors and non-survivors with the latter demonstrating a higher white blood cell count and a lower absolute lymphocyte and T cell count.

Commentary

Using the Joanna Briggs Institute Critical Appraisal tool for systematic reviews, ten out of the eleven criteria were judged to be satisfactory or not applicable for this review ⁽⁷⁾. The criterion which was not achieved was the inclusion criteria, which was deemed inappropriate for the clinical question. Due to the lack of clarity for inclusion criteria related to population, it is unclear how hospitalised COVID-19 patients were defined. Subsequently, caution needs to be used when interpreting the results for completeness and external validity. Without specific definitions of these terms, it is unclear what was defined as hospital care and what methods of diagnosis were required to be classified as a COVID-19 patient.

This systematic review identified that a quarter of patients hospitalised with COVID-19 subsequently died and a significant proportion of these patients were men and older adults (on average 15 years older than the survival group). The two most prevalent comorbidities amongst hospitalised patients were hypertension (43.6%) and diabetes (23.8%) and of those patients who died, these comorbidities were present in 56.8% and 31.2% respectively. The odds of dying were 2.5 times more if hypertension was present and 2 times more for diabetes. CHD/cardiovascular disease was associated with a 3.8 times greater risk of mortality and was found to be present in approximately 12% of COVID-19 hospitalised patients. A recent systematic review⁽⁸⁾ concurs with these findings that older age, hypertension, and diabetes mellitus conferred a significantly increased risk of mortality. Therefore, the presence of these comorbidities may be used to help inform resource management, risk stratification and subsequent management of hospitalised COVID-19 patients.

The findings from the review suggest that the associations between cardiovascular disease and COVID-19 may be due to infection related ischemia leading to myocardial injury and/or viral induced inflammatory processes. Indeed, the results of the review showed that biomarkers for myocardial injury and increased inflammation were higher on admission in the non-survival group. Other biomarkers on admission suggested a greater prevalence of end organ dysfunction, inflammation and coagulopathy in those that did not survive. Similar findings were identified in a recent study of diabetes patients hospitalised with COVID-19. In the study, nearly all biological covariates reflecting COVID-19 severity were associated with death, including admission plasma glucose, plasma

creatinine, AST, white cells, lymphocyte, platelet counts and CRP level ⁽⁹⁾. This highlights the importance of admission biomarkers in identifying those at greater risk of mortality and providing appropriate treatment.

The review suggests that COVID-19 may have a direct effect on endothelial dysfunction and a subsequent reduction in the ability to produce nitric oxide, similar to other infections within the Severe Acute Respiratory Syndrome (SARS) family of viruses. The review implies that should an underlying endothelial dysfunction be present (an early event in hypertension, diabetes, CHD and kidney dysfunction) that it is possible for COVID-19 to cause further damage, leading to poorer outcomes and death. The authors acknowledge that further research in this area is required.

As new studies continue to be published in this priority area, systematic reviews should be regularly updated to build on the findings identified in other geographical areas. It is also important to clearly identify who the patients of the included studies are in terms of demographics, details of hospitalisation (including severity of condition on admission), location of patients within the hospital (COVID-19 ward or ICU) and how comorbidities/biomarkers are assessed and collected (patient record, swab test etc.). This will enable clearer recommendations to be made in the hospital management of COVID-19 patients.

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