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Review

Hypocalcemia is associated with severe COVID-19: A systematic review and meta-analysis

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ABSTRACT

Background and aims: Hypocalcemia is commonly in critically ill patients and studies have shown that hypocalcemia is prevalent in patients with COVID-19. This meta-analysis aimed to evaluate the prognostic performance of hypocalcemia in patients with coronavirus disease 2019 (COVID-19).

Methods: We performed a systematic literature search on PubMed, Scopus, and Embase with keywords "SARS-CoV-2" OR "COVID-19" OR "2019-nCoV" AND "hypocalcemia" up until 10 December 2020. The key exposure was hypocalcemia, defined as serum calcium below study-defined cut-off points. The main outcome was poor outcome, which was a composite of mortality and severity. The effect estimate of the main outcome was reported as odds ratio (OR) and its 95% confidence interval (95% CI). We also generate sensitivity, specificity, positive and negative likelihood ratio (PLR & NLR), diagnostic odds ratio (DOR), and area under curve (AUC).

Results: There are 2032 patients from 7 studies included in this systematic review and meta-analysis. The incidence of poor outcome in this study was 26%. Serum calcium was lower in patients with poor outcome (mean difference -0.173 mmol/L [$-0.259, -0.087$], $p < 0.001$; $I^2: 31.3\%$). Hypocalcemia was associated with poor outcome (OR 3.19 [2.02, 5.06], $p < 0.001$; $I^2: 32.86\%$); with sensitivity of 0.74 [0.53, 0.88], specificity of 0.54 [0.29, 0.77], PLR of 1.6 [1.1, 2.3], NLR of 0.49 [0.35, 0.66], DOR of 3 [2, 5], and AUC of 0.70 [0.66, 0.74]. In this pooled analysis, the post-test probability was 36% in patients with hypocalcemia and 15% in patients without hypocalcemia.

Conclusion: Hypocalcemia was associated with poor outcome in COVID-19 patients.

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1. Introduction

Clinical presentation in patients with coronavirus Disease-2019 (COVID-19) ranges from mild to critical, with multiple complications requiring ventilator support [1,2]. Patients with comorbidities are at higher risk of developing a more severe condition [3–7]. Simple and non-invasive assessments are helpful to identify

patients at higher risk for severe outcome that requires more intensive monitoring and respiratory support. This is of the essence, especially in developing countries.

Hypocalcemia is commonly observed in critically ill patients and is associated with increased mortality [8–11]. Studies have shown that hypocalcemia is prevalent in patients with COVID-19 and is potentially associated with poor prognosis [12,13]. This meta-analysis aimed to evaluate the prognostic performance of hypocalcemia in patients with coronavirus disease 2019 (COVID-19).

2. Material and methods

This is a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines compliant meta-analysis. The protocol of this meta-analysis is registered at PROSPERO (CRD42020225506).

Abbreviations: COVID-19, Coronavirus Disease 2019; ICU, Intensive Care Unit; IMV, Invasive Mechanical Ventilation; NLR, Negative Likelihood Ratio; OR, Odds Ratio; PLR, Positive Likelihood Ratio; SROC, Summary Receiver Operating Characteristic.

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2.1. Eligibility criteria

We include all observational, both prospective and retrospective studies on patients with COVID-19 that reported (1) hypocalcemia and (2) mortality/severity/need for intensive unit care (ICU)/critical care/invasive mechanical ventilation (IMV). We excluded abstract-only studies, commentaries, preprints, case reports, and non-English language articles.

2.2. Search strategy and study selection

We performed a systematic literature search on PubMed, Scopus, and Embase with keywords “SARS-CoV-2” OR “COVID-19” OR “2019-nCoV” AND “hypocalcemia” up until 10 December 2020. The MEDLINE (PubMed) search keywords were ((SARS-COV-2) OR (COVID-19) OR (2019-nCoV) AND Hypocalcemia). Two independent authors performed screening of the title/abstracts after removal of duplicates. Discrepancies were resolved by discussion.

2.3. Data extraction

Two individual authors performed data extraction from the included studies, the data was recorded in standardized extraction forms. Details on first author, study design, year, age, male gender, diabetes, hypertension, hypocalcemia cut-off points, and outcome of interest were obtained.

The key exposure was hypocalcemia, defined as serum calcium below study-defined cut-off points. The main outcome was poor outcome, which was a composite of mortality and severity. Severe COVID-19 was defined as patients with COVID-19 who fulfill the criteria for severe CAP12 and need ICU/critical care/IMV.

The effect estimate of the main outcome was reported as odds ratio (OR) and its 95% confidence interval (95% CI). The mean difference in serum calcium between those with poor outcome and without was calculated. We also generate sensitivity, specificity, positive and negative likelihood ratio (PLR & NLR), diagnostic odds ratio (DOR), and area under curve (AUC).

2.4. Risk of bias assessment

Two independent authors assess the risk of bias of the included studies using the Newcastle-Ottawa Scale (NOS), discrepancies that arised was resolved by discussion.

2.5. Statistical analysis

We use STATA 16 (Stata Corp) software to perform meta-analysis. Meta-analysis of proportion was performed to pool incidence/prevalence. Restricted-maximum likelihood (REML) random-effects meta-analysis was used to calculate (1) OR and its 95% CI, (2) mean difference and its 95% CI. The effect estimate was considered significant if the p-value was below 0.05. I-squared (I^2) and Cochran Q test was used to assess heterogeneity, a value of <50% or $p < 0.10$ indicates significant heterogeneity. For the diagnostic test accuracy meta-analysis, sensitivity, specificity, PLR, NLR, DOR, and AUC were pooled. Funnel-plot and Egger's t -test were performed to assess publication bias. Trim-and-fill analysis using Run (RO) estimator was performed. REML meta-regression was performed for the association between hypocalcemia and poor outcome, using age, gender (male), diabetes, and hypertension as covariates, one at a time.

3. Results

3.1. Study selection and baseline characteristics

There are 2032 patients from 7 studies included in this systematic review and meta-analysis [12–18] (Fig. 1). The characteristics of the included studies and the risk of bias assessment of individual studies are displayed in Table 1. The prevalence of hypocalcemia in the included studies was 55% (23–87%). The incidence of poor outcome in this study was 26%.

3.2. Hypocalcemia and poor outcome

Serum calcium was lower in patients with poor outcome (mean difference -0.173 mmol/L [$-0.259, -0.087$], $p < 0.001$; $I^2: 31.3\%$, $p = 0.354$) [Fig. 2]. Hypocalcemia was associated with poor outcome (OR 3.19 [2.02, 5.06], $p < 0.001$; $I^2: 32.86\%$, $p = 0.276$) [Fig. 3]. Hypocalcemia was associated with sensitivity of 0.74 [0.53, 0.88], specificity of 0.54 [0.29, 0.77], PLR of 1.6 [1.1, 2.3], NLR of 0.49 [0.35, 0.66], DOR of 3 [2,5], and AUC of 0.70 [0.66, 0.74] [Fig. 4]. Fagan's nomogram indicate that in this pooled analysis, the post-test probability was 36% in patients with hypocalcemia and 15% in patients without hypocalcemia [Fig. 5].

3.3. Publication bias

The association between hypocalcemia and poor outcome has a symmetrical funnel-plot and egger's test showed indication of small-study effects ($p = 0.042$). Trim-and-fill analysis using Run RO estimator resulted in OR of 2.54 [1.85, 3.49] after imputation to the left side of the funnel plot.

3.4. Meta-regression

Meta-regression analysis indicates that the association between hypocalcemia and poor outcome was influenced by hypertension (OR 0.96 [0.93, 1.00], $p = 0.47$), but not age ($p = 0.383$), male gender ($p = 0.071$), and (diabetes $p = 0.114$).

4. Discussion

This meta-analysis indicates that hypocalcemia was associated with mortality in patients with COVID-19 with 74% sensitivity, 58% specificity, and AUC of 0.71.

The heterogeneity in the pooled analysis is low-moderate despite slight difference in cut-off points. Meta-regression analysis showed that hypertension modify the association between hypocalcemia and mortality. Ideally, meta-regression analysis requires at least 10 studies to attain statistical power. This serves as a preliminary finding that requires confirmation in further studies. Previously, a propensity-score matched cohort indicate that plasma calcium was associated with the incidence of hypertension [19], indicating that there might be a mechanistical link in the current finding. Additionally, patients with hypertension are at higher risk of developing CKD and vice versa. In patients undergoing hemodialysis, hidden hypercalcemia was associated with increased mortality [20]. Unfortunately, there is only one study that clearly reported the presence of CKD, thus subsequent analysis cannot be performed. Alternatively, the finding of meta-regression might be just an incidental finding.

Hypocalcemia has been shown to be associated with mortality in hospitalized patients [21]. Decreased dietary intake, over-secretion of parathyroid hormone, hypoproteinemia, vitamin D deficiency, drug interactions may cause hypocalcemia in critically ill patients [22]. One of the included study shown that in the acute phase of COVID-19, hypoproteinemia, and imbalanced parathyroid

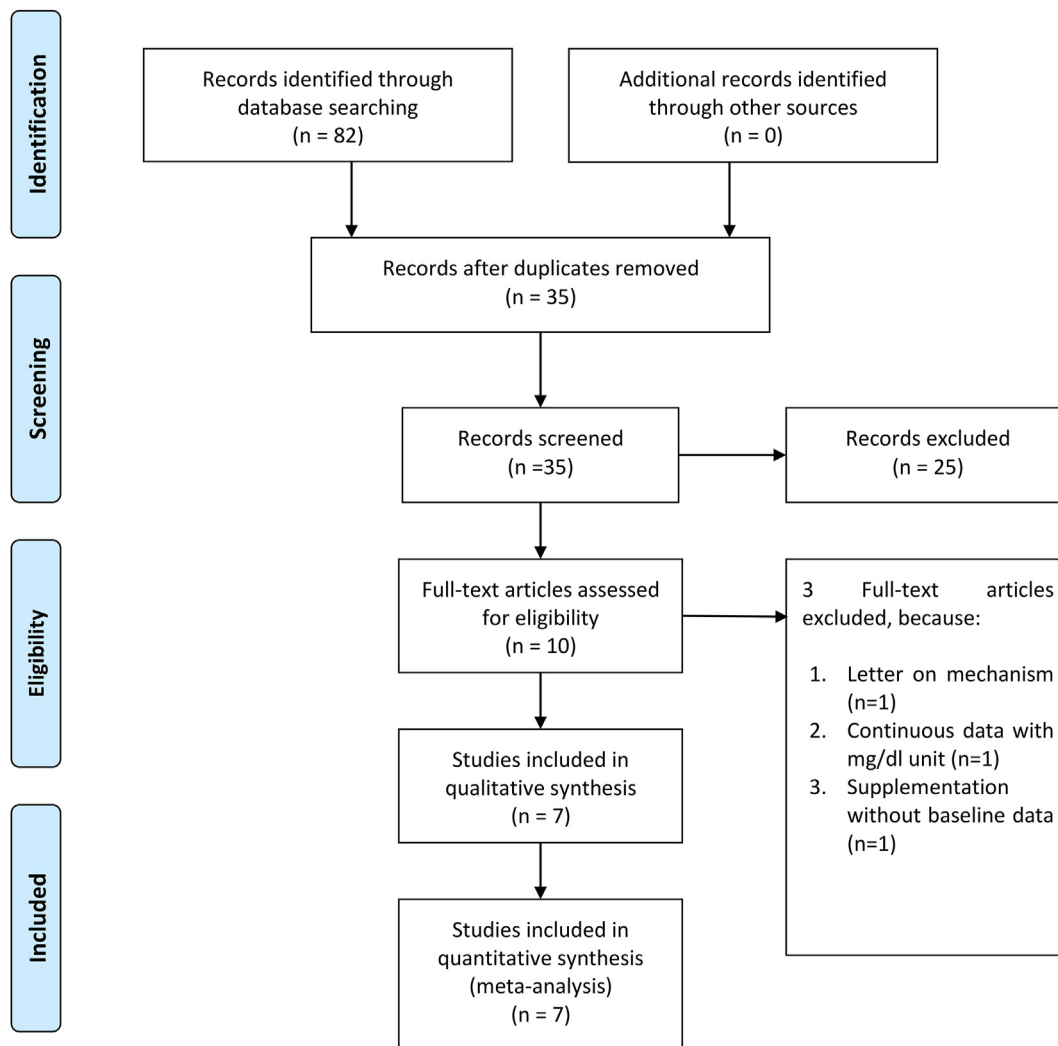


Fig. 1. PRISMA flowchart.

Table 1
Baseline characteristics of the included studies.

First Author	Study Design	Sample	Hypocalcemia Cut-off Value (mmol/L)	Outcome	Age	Male	Diabetes	Hypertension	CKD	NOS
Filippo L 2020	RC	531	–	Mortality	59	67.8	13.7	33.3	–	8
Liu J 2020	RC	107	<2.15	ICU/IMV/Death	68	49	19	37	–	8
Lu L 2020	RC	304	–	IMV	44	59.9	–	–	–	6
Sun J 2020	RC	241	<2.00	Mortality	65	46.5	–	–	–	6
Tezan M 2020	RC	408	<2.12	Mortality	54.3	46.1	23.5	31.9	3.2	6
Torres B 2020	RC	316	–	ICU Care	65	65	16	51	–	6
Wu Y 2020	RC	125	<2.20	Prolonged Hospitalization	55	52.8	20	28	–	8

CKD: Chronic Kidney Disease; NOS: Newcastle-Ottawa Scale; RC: Retrospective Cohort.

hormone and vitamin D were associated with hypocalcemia [15]. The rate of hypocalcemia was higher in patients with COVID-19 compared to non-COVID-19 respiratory illness despite similar baseline characteristics [13], indicating that hypocalcemia might be more distinctive in coronavirus infections [23]. Additionally, hypocalcemia in critically ill patients might be caused by other complications such as acute renal insufficiency, pancreatitis, and alkalosis; which may lead to poor prognosis [22]. Chronic renal and liver disease may also cause hypocalcemia and these were associated with poor prognosis in COVID-19 [24]. Vitamin D deficiency might also be found more frequently in the elderly patients and in

those with less exposure due to reasons such as comorbidities and frailty, which themselves, are associated with mortality [25–27]. Higher proportion of COVID-19 patients with hypocalcemia requires high oxygen support requirement [17]. All of the included studies uniformly showed a significant association between hypocalcemia and mortality.

4.1. Clinical implications

Hypocalcemia can be used as one of predictor of poor outcome in patients with COVID-19. However, it is better used as one of

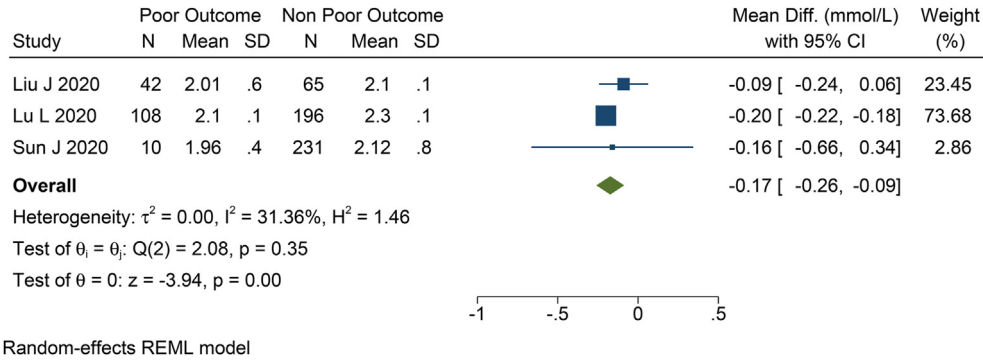


Fig. 2. Forest-plot for hypocalcemia and composite poor outcome.

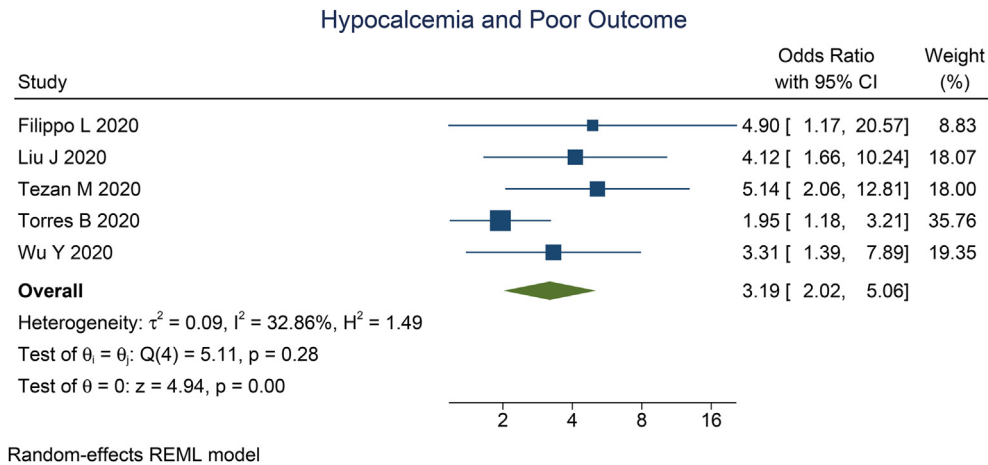


Fig. 3. Pooled sensitivity and specificity.

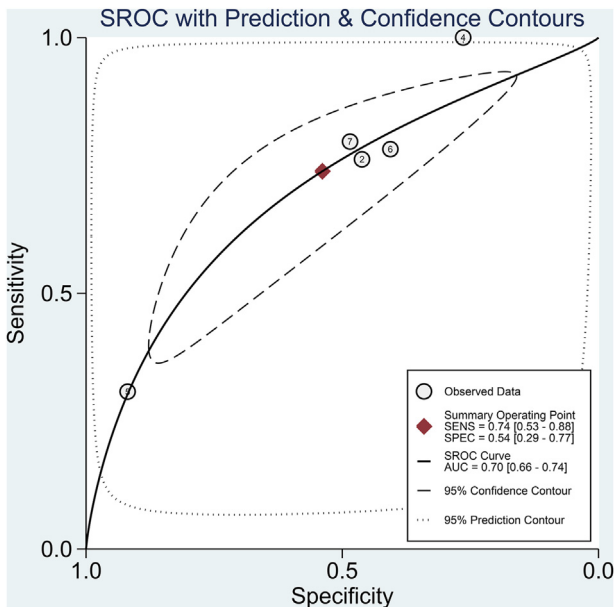


Fig. 4. SROC with prediction & confidence contours.

4.2. Limitation

The main limitation of this study is due to the small number of studies, thus, only meta-regression with limited power can be performed. The finding associated with meta-regression is preliminary and needs to be confirmed by further studies. Additionally, all of the studies were retrospective in design and at higher risk of bias. Most of the included studies also did not report the percentage of CKD patients, which may potentially confound the association.

5. Conclusion

Hypocalcemia was associated with poor outcome in COVID-19 patients.

Contributorship statement

JWM and RP were involved in the conceptualization and design of the manuscript. JWM, AW, and RP participated in data curation and investigation. RP performed data analysis, formal analysis, and statistical analysis. AW and RP drafted the manuscript. JW review and edited the manuscript.

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markers in a prediction model, rather than used alone. Whether calcium supplementation will be beneficial in patients with hypocalcemia requires further investigations.

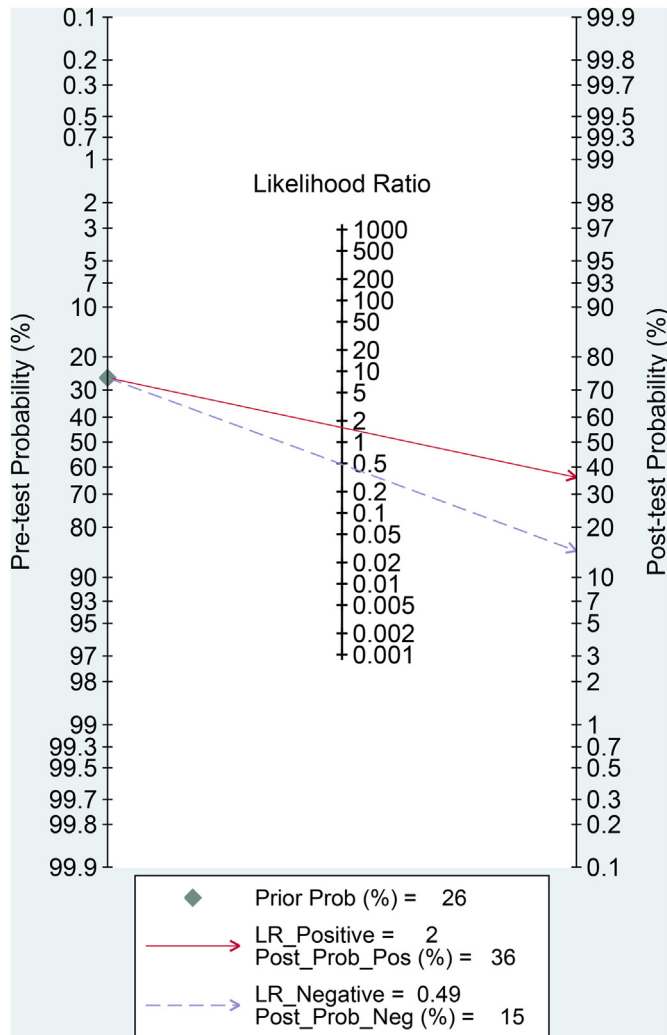


Fig. 5. Fagan's nomogram.

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Ethical approval

Not Applicable.

Informed consent

Not Applicable.

Data availability

Data are available on reasonable request.

Declaration of competing interest

The authors declared no conflict of interest.

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