Prognostic associations of ECG tracings in hospitalised patients with COVID-19: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction COVID-19 is a global pandemic caused by the SARS-CoV-2 virus. Although most COVID-19 cases are asymptomatic or mild, a significant number of patients experienced adverse outcomes. In addition, studies have shown that cardiac abnormalities are associated with increased mortality in hospitalised patients with COVID-19. This finding sets a precedent for the potential use of ECG tracing as an indicator of patient mortality and morbidity. This study aims to determine associations between the 12-lead ECG findings and various clinical outcomes of hospitalised patients with COVID-19, measured as incidence of endotracheal intubation, intensive care unit (ICU) admission and mortality rate.

Methods and analysis An electronic literature search will identify all potentially relevant articles using specific databases and websites. The search will be limited to studies published from December 2019 to May 2021. In addition, studies will include hospitalised patients with COVID-19 with normal and abnormal 12-lead ECG findings assessed for clinical outcomes, including the incidence of endotracheal intubation, ICU admission and mortality rate. The risk of bias in individual studies will be evaluated using the Quality in Prognostic Studies tool or the Cochrane risk of bias tool. A meta-analysis will be conducted if at least two studies indicate a prognostic factor’s effect. Moreover, subgroup and sensitivity analyses will be performed accordingly to address heterogeneity. Reporting the review results will comply with the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. The quality of evidence generated will be assessed using the Grades of Recommendation, Assessment, Development and Evaluation system.

Ethics and dissemination This study has been exempted from ethics review. There will be no patient or public involvement in this study. Furthermore, the findings will be disseminated via conferences, seminars, symposia and congresses on top of peer-reviewed journals.

INTRODUCTION

The COVID-19 is a global pandemic declared by the WHO on 11 March 2020. It is caused by the SARS-CoV-2 virus, which mainly spreads through droplets and aerosols and is primarily diagnosed via a reverse transcription-PCR (RT-PCR) of a nasopharyngeal swab. Since its emergence, it has already caused approximately 572 million cases and 6.4 million deaths as of writing.

Although most COVID-19 cases are asymptomatic or mild, a significant number of patients experience adverse outcomes like hospitalisation, intubation and death. Furthermore, it poses numerous complications, significantly affecting patient prognosis. Recent reports, for example, have revealed that cardiac complications are frequent among patients with COVID-19, and these are commonly associated with worsened severity and increased mortality.
Another study suggested that identifying specific ECG tracings associated with COVID-19 is vital in predicting adverse outcomes. Previous studies have shown that prolongation in heart rate-corrected QT interval in ECG findings was observed due to medications.\textsuperscript{6,7} ECG may provide significant prognostic value for primary adverse outcomes, resulting from COVID-19 infection,\textsuperscript{8} as demonstrated by another study wherein it reported on the predictive value of admission ECG in patients with COVID-19.\textsuperscript{9}

Since COVID-19 is a relatively new disease, specific treatment strategies have not yet been established. Therefore, the treatment approaches heavily rely on the clinician’s experience and decision-making skills. This systematic review and meta-analysis aimed to assess the utility of ECG—an easy, routine bedside procedure—to help identify high-risk patients with COVID-19. In addition, this method will guide clinicians in stratifying management by determining further what specific ECG tracings are prognostic of the clinical outcomes of patients with COVID-19. And finally, this systematic review and meta-analysis will give the clinicians and researchers more information regarding the diversity in patterns observed in the ECG of patients with COVID-19 in comparison with COVID-19 patients with no known cardiac diseases. This diversity of ECG patterns may be attributable to the effect of COVID-19 infection and certain medications, which may be answered by our study.

**STUDY AIMS**

The main objective of this study is to determine if there is an association between the 12-lead ECG findings and clinical outcomes of hospitalised patients with COVID-19. Specifically, this study aims to determine the clinical outcomes of hospitalised patients with COVID-19, with abnormalities in 12-lead ECG findings, in terms of:

1. Incidence of endotracheal intubation.
2. Incidence of intensive care unit (ICU) admission.
3. Mortality rate.

**METHODS AND ANALYSIS**

This protocol was designed based on the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P) guidelines,\textsuperscript{10} as illustrated in the PRISMA-P checklist (online supplemental file 1). Reporting of the results will be based on the PRISMA guidelines.\textsuperscript{11} This systematic review and meta-analysis will be implemented for about 6 months, from February to July 2022.

**Eligibility criteria**

**Types of studies**

Prospective and retrospective observational studies (case-control and cohort studies) and randomised controlled trials (RCTs) from December 2019 to May 2021 will be eligible for this review.

**Target population**

This study will include hospitalised SARS-CoV-2 RT-PCR-confirmed patients with COVID-19 aged 18 years and older.

**Types of index prognostic factors**

The prognostic factors to be assessed include abnormal 12-lead ECG findings such as tachycardia, bradycardia, ST-segment change, T-wave change, QT prolongation, atrial fibrillation, ventricular arrhythmia, conduction disorder, left anterior fascicular block, left bundle branch block, right bundle branch block, atrioventricular block, intraventricular block, left ventricular hypertrophy, atrial premature complex, ventricular premature complex and abnormal axis.

These will be compared with the clinical outcomes of hospitalised patients with COVID-19 with normal 12-lead ECG tracings.

**Outcome assessment**

The primary clinical outcomes will include the following:

1. Incidence of endotracheal intubation. Insertion of a plastic tube by way of the mouth down into the trachea to open the airway and facilitate oxygenation to the lungs.
2. Admission to the ICU. Transfer of the patient to the ICU of a hospital.
3. In-hospital COVID-19 mortality. Death of the patient in the hospital as declared by a qualified physician.

**Types of comparator prognostic factors**

As COVID-19 is a relatively new disease, limited prognostic models are available. Hence, no comparator prognostic models will be used for this study.

**Sources of information**

An electronic literature search will identify all potentially relevant articles using the specific databases and websites mentioned below. The search query used as the basis is specified in online supplemental file 2.

The search will be limited to studies published from December 2019 to May 2021. All studies will only be limited to articles published in the English language.

**Electronic searches**

Electronic databases (PubMed, Embase, Clinical Key, Cochrane Library, Science Direct, Trip Database, Health Research and Development Information Network (HERDIN), BioMed Central, ACCESSSSS Federated Search, PLoS One, Index Medicus for South-East Asia Region (IMSEAR), Global Index Medicus, Western Pacific Region Index Medicus (WPRIM), APAMED Central, Research4Life, CNKI), and the website, Google Scholar, will be used in finding journal articles.

**Searching other resources**

Bibliographic references of selected articles and related systematic reviews will be reviewed to identify potentially...
relevant articles that might be missed in the original search.

**Data collection and analysis**

**Data management**

Articles retrieved will be encoded in EndNote V.20 for collation of all articles and removal of all duplicates. After eliminating duplicates, the list of obtained articles will be exported to Covidence, where the screening process will be conducted. All accepted articles will be stored in password-protected storage using Google drive, and only the research team will be given access to these articles.

**Selection of studies**

Three review authors (JSI, JGG, and GSY) will screen the retrieved articles independently by appraising their titles and abstracts against the inclusion criteria. The following inclusion criteria will be used:

1. ECG tracings and COVID-19 clinical outcomes.
2. Prospective/retrospective observational studies.
3. RCTs.
4. Published from December 2019 to May 2021.
5. Not a duplicate of another study that had already been assessed for selection.
6. Published in the English language.
7. Studies with patients with no known cardiac diseases to act as baseline/comparator.

The following exclusion criteria will be used:

1. Case reports.
2. Case series.
3. Review articles.
4. Editorials.
5. Commentaries.
6. Blogs.
7. Studies published in abstract format only.
8. Studies with incomplete data.
9. Preprints.

All abstracts that meet the inclusion criteria will be appraised as full articles. Following a full-text review, preliminary articles that meet the inclusion criteria will be subjected to subsequent data analysis. The consensus of the three authors will be used to resolve any disagreements. If one research group conducted more than one study, the study with the largest study population would be included. The most recent publication will be included in prospective studies with multiple publications.

**Data extraction**

Three authors will extract the necessary data for studies that fulfill the inclusion criteria. Extracted data will then be stored in Google Sheets and EndNote V.20. The Google Sheet will be password-protected, and only the research team members will be given access to these records to protect the data. Before conducting the systematic review, a pilot test of the data extraction form will be done. Disagreements will be resolved by casting the majority vote among the authors. The extracted data will then be processed using RevMan V.5.4.1.

The following data items will be extracted:

- Title of the study.
- Author and publication: author’s name, publication year, country published in.
- Methods: study design, trial setting, duration of the study, date when the study was conducted.
- Targeted population: inclusion and exclusion criteria, number of enrolled participants, number of drop outs, number of participants who completed the study, number of participants lost to follow-up.
- Prognostic factors: characteristics of the prognostic factor assessed.
- Length of follow-up: duration of prognostic factor measurement to the time of outcome assessment.
- Outcomes: incidence of endotracheal intubation, ICU admission, in-hospital mortality.
- Statistical analyses: results of the statistical analyses performed on the study.
- Conclusion: conclusion as stated by the author/s of the included studies.

**Risk of bias assessment in individual studies**

Three review authors will independently assess the risk of bias (RoB) in each included study. Quality In Prognostic Studies tool for prognostic factor studies will be used. The following domains will be assessed: study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement and statistical analysis and reporting. The different domains will be evaluated depending on if the essential information regarding the domain has been disclosed (unsure, no, partial, yes). Subsequently, the review authors will make a concluding assessment on each domain’s RoB according to their evaluation (low, moderate, high). This will result in six RoB ratings, one for each domain, which will then be compared with the rating of the other review authors. Furthermore, each article will be categorised as having low, moderate, or high RoB. For this purpose, the following rating scale (table 1) will be used:

As for RCTs, the Cochrane RoB tool for RCTs will be used. The following domains will be assessed: random sequence generation, selective reporting, incomplete outcome data, the similarity of baseline characteristics, allocation concealment, blinding of participants, blinding of outcome assessment and other biases. The articles will

| Table 1 | Risk of bias (RoB) classification |
|---------|----------------------------------|
| **Classification of RoB** | Criteria |
| Low | All domains have low RoB or at most one has moderate RoB |
| Moderate | Anything in between |
| High | At least one domain has high RoB, or at least three domains have moderate RoB |

RoB, Risk of Bias.
be appraised for validity based on the following primary and secondary criteria:

- Primary criteria: randomisation, intention-to-treat analysis, adequacy of follow-up
- Secondary criteria: blinding, allocation concealment, the similarity of baseline characteristics

The methodological quality of the studies will be rated using the rating scale in Table 2.

**Measures of association**

The outcomes of the eligible studies will be acquired if available or otherwise be calculated. Continuous data will be expressed as mean differences with a 95% CI. Binary outcomes will be measured using relative risks (RRs), odds ratio (ORs) or hazard ratio (HRs); values are significant if the CI does not cross 1. ORs and HRs will be calculated from the absolute values of the outcome of interest across two groups being compared. ORs may also be acquired through logistic regression models. HRs will be calculated in studies presenting outcomes using the log-rank test, Cox’s proportional hazards models and the Kaplan-Meier survival curve.

**Dealing with missing data**

Studies with incomplete or missing data will be excluded as well as studies with authors of articles who are unavailable for further communication or uncontactable. The data relevant to our studies such as incidence of endotracheal intubation, ICU admission and mortality rate will be looked on. Studies with these lacking data will be excluded if all methods to extract them have already been exhausted. Furthermore, standard deviations (SDs) for mean changes that were not reported in the journal itself will be calculated using RevMan 5.4.1. Additionally, the imputation of missing data needed in the analysis will be approached according to the Cochrane Handbook for Systematic Reviews of Interventions.

**Comparison of effect estimates**

Due to the differences in study design and data analysis, effect estimates from observational studies and randomised control trials might not be directly comparable. A comparison of effect estimates from these research articles will be made using the approach proposed by the INSIGHT START Study Group. This approach will include harmonisation of the study protocols to ensure that the studies target the same causal effect, harmonisation of the data analysis to target a common estimand and sensitivity analyses to investigate the impact of any remaining discrepancies.

**Assessment of heterogeneity**

Heterogeneity will be assessed using (a) forest plot visual examination to examine the poor overlap between the individual CIs as indicative of heterogeneity, (b) standard $\chi^2$ test using p value <0.10 to test significance and (c) $I^2$ test to quantify inconsistency across all the studies. Results of $I^2$ test will be classified to four classes: (a) no significant heterogeneity (0% to 40%), (b) moderate heterogeneity (30% to 60%), (c) substantial heterogeneity (50% to 90%) and (d) considerable heterogeneity (75% to 100%). The importance of the observed value of $I^2$ depends on the magnitude and direction of effects and the strength of evidence for heterogeneity. In addition, a random effects model, subgroup analysis and sensitivity analysis will be used to address heterogeneity.

**Assessment of reporting deficiencies**

Publication and other reporting biases will be minimised through a comprehensive search for literature, including unpublished studies. Publication bias will be gauged by funnel plot analysis and Egger’s test should there be ≥20 studies included. Statistical significance will be based on a p value of <0.10. If publication bias is noted, the trim and fill method will be employed to minimise the publication bias’ impacts on the effect estimates of the remaining studies. In this method, the studies that cause asymmetry in the funnel plot will be trimmed. Then the imputed missing studies will be filled in according to the bias-corrected overall estimate.

**Data synthesis**

**Data synthesis and meta-analysis approaches**

Prognostic factors, reported by at least two separate studies and measured the outcome of interest as stated above, will be included for further statistical analyses. A meta-analysis will be performed if the studies are sufficiently robust and comparable. RevMan V.5.4.1 will be used to conduct the meta-analysis. Outcomes with continuous data will be pooled as a mean difference if they have the same unit of measurement or standardised mean difference (Hedge’s g) if they have different units of measurement. Continuous variables presented as a median, range or interquartile range (IQR) will be transmuted as mean values with their corresponding SD. Only unadjusted effect estimates will be pooled together. Multivariate models will not be reported quantitatively as adjustments in the model might lead to misleading pooling of the data. Instead, a qualitative assessment will be done. A fixed-effects model will be initially used to analyse the data if a meta-analysis is possible with the collated data. In addition, the random-effects model will be used as necessary to account for heterogeneity. Statistical significance will be based on a p value <0.05, and the 95% CI will be used. If data cannot be combined due to the inadequate number of studies or sheer heterogeneity due to clinical and methodological variability among studies, qualitative analysis will be done instead.
Confirmation of prognostic factors
The final prognostic ECG tracings for clinical outcome assessment of hospitalised patients with COVID-19 will be identified for result consistency and statistical significance in both univariate and multivariate analyses.23 First, putative prognostic factors will be determined by checking if the trend is consistent across all univariate analyses reporting said factors, and it is statistically significant in at least 60% of the studies. Additionally, the identified putative prognostic factors will be cross-checked against effect estimates from multivariate analyses.23

Subgroup analysis and investigation of heterogeneity
The following subgroups will be used for subsequent analyses to investigate heterogeneity:
► The age group of the participants.
► Timing of outcome measurement.
► Type of intervention given to the patient.
► The sample size of the studies.
► Study type.

Sensitivity analysis
Sensitivity analysis will be performed by excluding studies with poor quality as determined by the RoB assessment. This analysis will be performed to evaluate the robustness of the results.

Rating the certainty of evidence and summary of findings
The overall quality and credibility of the findings will be evaluated using the Grades of Recommendation, Assessment, Development and Evaluation system. Under this system, five domains—RoB, imprecision, inconsistency, indirectness and publication bias—will be rated as very low, low, moderate and high based on certainty.21 24

Participant and public involvement statement
The participants and the public were not involved in the design and implementation of the protocol.

Ethics and dissemination
There is no need for this study to acquire an ethical approval because no private information of participants will be involved. Results of the present study will be disseminated in a peer-reviewed journal or conference presentation. Important protocol amendments will be documented and updated on PROSPERO.

DISCUSSION
The COVID-19 pandemic caused by SARS-CoV-2 is characterised by an increased mortality rate due to acute interstitial pneumonia and severe respiratory distress syndrome.25–27 It is suggested that cardiac injury is evident among 20%–30% of the patients with COVID-19.28 Cardiac injury was characterised by arrhythmias and elevated cardiac troponin T blood levels that are correlated with adverse clinical outcomes.29–31 This article presents the rationale and proposed methodology for conducting a systematic review and meta-analysis on the prognostic associations of ECG findings to the clinical outcomes of hospitalised patients with COVID-19.

Our protocol will present the analysis of research articles using a simple standard ECG, which can be easily acquired on admission of patients, and be helpful in recognising hospitalised patients with COVID-19 with adverse clinical outcomes. It has been previously demonstrated that most abnormalities in the ECG findings were significantly associated with death.32 Our meta-analysis study may also be useful to present a synthesis to stratify patients by showing short-term changes such as possible new arrhythmias or ST-segment/T wave abnormalities and explaining long-term cardiac abnormalities. These abnormalities have been suggested to predict negative outcomes in patients.4 33

Limitations
Several unavoidable methodological limitations must be recognised and considered to make an appropriate interpretation of the study findings and finally arrive at a supported conclusion. In this study, it is our aim to include only patients with no known cardiac diseases and use this as a baseline/comparator. This is under the assumption that those patients without known cardiovascular comorbidities have normal ECG. This is the best and most practical compromise given the limitations we have in clinical practice such that not all patients have baseline ECG tracings. Second, due to the multitude of databases to be searched and the wide range of search terms and queries that will be used to obtain relevant studies, obtained studies might have a high degree of heterogeneity in terms of study type, methodology, participants, estimates reported, outcomes and time points on which the outcomes under study were measured across the studies. Heterogeneity among studies will not only complicate the data analysis, but might also restrain the statistical power of possible meta-analyses if there are. Hence, it will limit the generalizability of the findings. In addition, our study will only include research articles published in the English language. It will not have other research outputs such as unpublished papers, grey literature and conference abstracts. Finally, the inherent limitation of our protocol includes the assumption that all patients in the included articles were in a standard supine position when ECG measurements were taken. Despite these methodological limitations, conducting a systematic review and meta-analysis on the said topic is vital, especially when the COVID-19 pandemic continues to cause significant morbidity and mortality globally.

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Acknowledgements We acknowledge the support and funding from St. Luke’s Medical Center (SLMC).
Contributors JSI conceptualised the topic and supervised the conduct of the research. JSI designed the rough protocol. JGG and GSGY critically reviewed the protocol design. JSI, JGG and GSGY wrote the initial manuscript and revised the manuscript as needed. JSI, JGG and GSGY defined the criteria for screening studies for this review, the types of outcomes to be looked at, the search methods, and the data collection and analysis process. JSI, JGG and ESB reviewed and revised the
manuscript and finalised the statistical analyses to be performed. AL and FG served as scientific advisors.

**Funding** This research will be funded by the St. Luke’s Medical Center (SLMC).

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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**Author note** If there is a need to amend this protocol, the date of each amendment and the reason for the change will be described.

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