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Charlson comorbidity index and a composite of poor outcomes in COVID-19 patients: A systematic review and meta-analysis

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ABSTRACT

Background and aims: The ongoing COVID-19 pandemic is disproportionately affecting patients with comorbidities. Therefore, thorough comorbidities assessment can help establish risk stratification of patients with COVID-19, upon hospital admission. Charlson Comorbidity Index (CCI) is a validated, simple, and readily applicable method of estimating the risk of death from comorbid disease and has been widely used as a predictor of long-term prognosis and survival.

Methods: We performed a systematic review and meta-analysis of CCI score and a composite of poor outcomes through several databases.

Results: Compared to a CCI score of 0, a CCI score of 1–2 and CCI score of ≥ 3 was prognostically associated with mortality and associated with a composite of poor outcomes. Per point increase of CCI score also increased mortality risk by 16%. Moreover, a higher mean CCI score also significantly associated with mortality and disease severity.

Conclusion: CCI score should be utilized for risk stratifications of hospitalized COVID-19 patients.

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1. Introduction

Since the emergence of Coronavirus Disease 2019 (COVID-19) in Wuhan in late December 2019, the total of confirmed cases and deaths of this contagious respiratory disease keeps increasing worldwide. As of July 17, 2020, the World Health Organisation (WHO) has declared more than 13 million people as a positive confirmed COVID-19 case that results in more than 580,000 deaths [1]. Through descriptive observational studies, it is well established that patients with comorbidities are disproportionately affected by COVID-19 and associated with worse clinical outcomes [2–5].

Therefore, it is crucial to have a thorough assessment of comorbidities to establish risk stratification of patients with

COVID-19 upon hospital admission. Charlson Comorbidity Index (CCI) is a validated, simple, and readily applicable method of estimating the risk of death from comorbid disease and has been widely used as a predictor of long-term prognosis and survival [6–8]. Thus, to delineate better the advantage of using CCI for risk stratifications in COVID-19 patients, we performed a systematic review and meta-analysis aimed to assess the association between CCI and a composite of poor outcomes in COVID-19 patients.

2. Methods

2.1. Search and selection criteria

A systematic literature search was performed through several databases, including Pubmed, EuropePMC, EBSCOhost, Proquest, Cochrane library and two preprint servers (preprint.org and Medrxiv). The keywords used were (“Charlson Comorbidity Index” OR “CCI” OR “Charlson Index”) AND (“COVID-19” OR “SARS-CoV-2” OR “Novel Coronavirus” OR “2019-nCov”). The inclusion criteria of

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Abbreviations

COVID-19	Coronavirus disease of 2019
CCI	Charlson comorbidity index
ORs	Odd Ratios
HRs	Hazard Ratios
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
MD	Mean difference
SIDIAP	System for Research In Primary Care
ACE-2	angiotensin-converting enzyme-2
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
TMPRSS2	Transmembrane protease serine 2
RAS	Renin-angiotensin system
NSAID	Nonsteroidal anti-inflammatory drugs
CRP	C-reactive protein
ICU	Intensive care unit

this study were studies of COVID-19 patients that reported any of the following: (1) odds ratios (ORs) and hazard ratios (HRs) of CCI score with a composite of poor outcomes (2) Mean CCI score for a composite of poor outcomes vs. no outcome, (3) per point HRs or ORs of CCI score and mortality. A composite of poor outcomes consists of mortality, need for critical care, severe disease presentation, mechanical ventilation. If two or more studies are consisting of the same population, we select the study that reported the most complete data regarding the inclusion criteria. We excluded: review articles, non-research letters, communications, and commentaries; studies with samples <20; case reports and small case series; non-English language articles; research in pediatric populations (17 years of age and younger). We finalized our systematic search on July 15, 2020. The search was performed by two independent researchers (JH and SL), and discrepancies were resolved by discussion with a third person (RP). This systematic search is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

2.2. Data extraction

Data extraction was carried out by JH, RP, and SL using a standardized form containing the following details: author name, country, study design, number of subjects, sex, age, outcome, and CCI score types. Data of CCI score that was reported other than mean \pm SD was transformed accordingly using a calculator available online, derived from Wan et al. and Luo et al. studies [9–11]. The risk of bias of the included studies was assessed using the Newcastle-Ottawa Score by 2 independent authors and discrepancies were resolved via discussion [12].

2.3. Statistical analysis

Review Manager 5.4 was used for the meta-analysis [13]. To characterize the association between CCI score (1–2 and ≥ 3) and a composite of poor outcomes, and per point CCI score and mortality, we calculated the pooled estimates and its 95% confidence interval in the form of odds ratios (ORs) and hazard ratios (HRs), respectively, using the generic inverse variance method. The CCI 0 was used as the reference of comparison. Whereas, to characterize the association between a composite of poor outcomes and mean CCI score, we calculated the pooled estimates in the form of a mean difference (MD) and its standard deviation. To account for

interstudy variability regardless of the heterogeneity, a random-effects model was assigned. We used two-tailed p values with a significance set at ~ 0.05 . To assess heterogeneity across studies, we used the inconsistency index (I^2) with a value above 50% or $p < 0.10$ indicates significant heterogeneity, whereas $I^2 < 25\%$ is considered low heterogeneity. Each individual component of the composite of poor outcomes was then sub-analyzed. A sensitivity analysis using the leave-one-out method was set to assess statistical robustness and detect the source of heterogeneity. Finally, an inverted funnel-plot analysis was used to detect any publication bias qualitatively.

3. Results

3.1. Study selection and characteristics

Figure one shows the study profile. A total of 20 studies were included in the qualitative and quantitative synthesis (Fig. 1, Table 1) [2,14–32]. One study which we included described an OR value. Nonetheless, we imputed it as an HR, because the other studies included defining the prognostic of per point CCI score and mortality used ORs.

3.2. The prognosis of CCI score 1–2 on mortality

A total of three studies showed that CCI 1–2 was significantly associated with mortality compared to CCI 0. The pooled HR was 1.41 [1.27, 1.57; $p < 0.001$] with high heterogeneity between studies [I^2 , 64%; $p = 0.04$] (Fig. 2). Upon sensitivity analysis by removing Burn (2) et al. study, heterogeneity can be reduced while maintaining the significant association with mortality (HR 1.33 (1.28, 1.39), $p < 0.001$; I^2 0%, $p = 0.46$) are still maintained.

3.3. The prognosis of CCI score ≥ 3 on mortality

A total of three studies showed that CCI ≥ 3 was significantly associated with mortality (HR 1.77 (1.68, 1.86), $p < 0.001$; I^2 0%, $p = 0.62$) (Fig. 3).

3.4. Per point CCI score and mortality

Pooled HRs across four studies showed a non-significant association between increased per point CCI score and mortality (HR 1.09 (0.97, 1.23), $p = 0.13$; I^2 77%, $p = 0.005$). Moreover, upon removal of Price-Haywood study, heterogeneity can be reduced, indicating statistical robustness while maintaining significant associations (HR 1.16 (1.07, 1.25), $p < 0.001$; I^2 0%, $p = 0.50$) (Fig. 4).

3.5. The association between CCI score 1–2 and a composite of poor outcomes

A total of two studies showed that CCI 1–2 was significantly associated with a composite of poor outcomes (mortality and disease severity) (OR 1.90 (1.61, 2.24), $p < 0.001$; I^2 0%, $p = 0.47$) (Fig. 5).

3.6. The association between CCI score ≥ 3 and a composite of poor outcomes

A total of two studies showed that CCI ≥ 3 was significantly associated with a composite of poor outcomes (mortality and disease severity) (OR 2.95 (2.39, 3.65), $p < 0.001$; I^2 28%, $p = 0.23$) with considerable subgroup differences (I^2 72.8%, $p = 0.06$). Furthermore, subgroup analysis showed that CCI score ≥ 3 was significantly associated with mortality (OR 3.51 (2.69, 4.57), $p < 0.001$; I^2 0%, $p = 0.44$) and disease severity (OR 2.49 (1.97, 3.13), $p < 0.001$; I^2 0%, $p = 0.61$) (Supplementary Fig. 1). Upon sensitivity analysis by removing

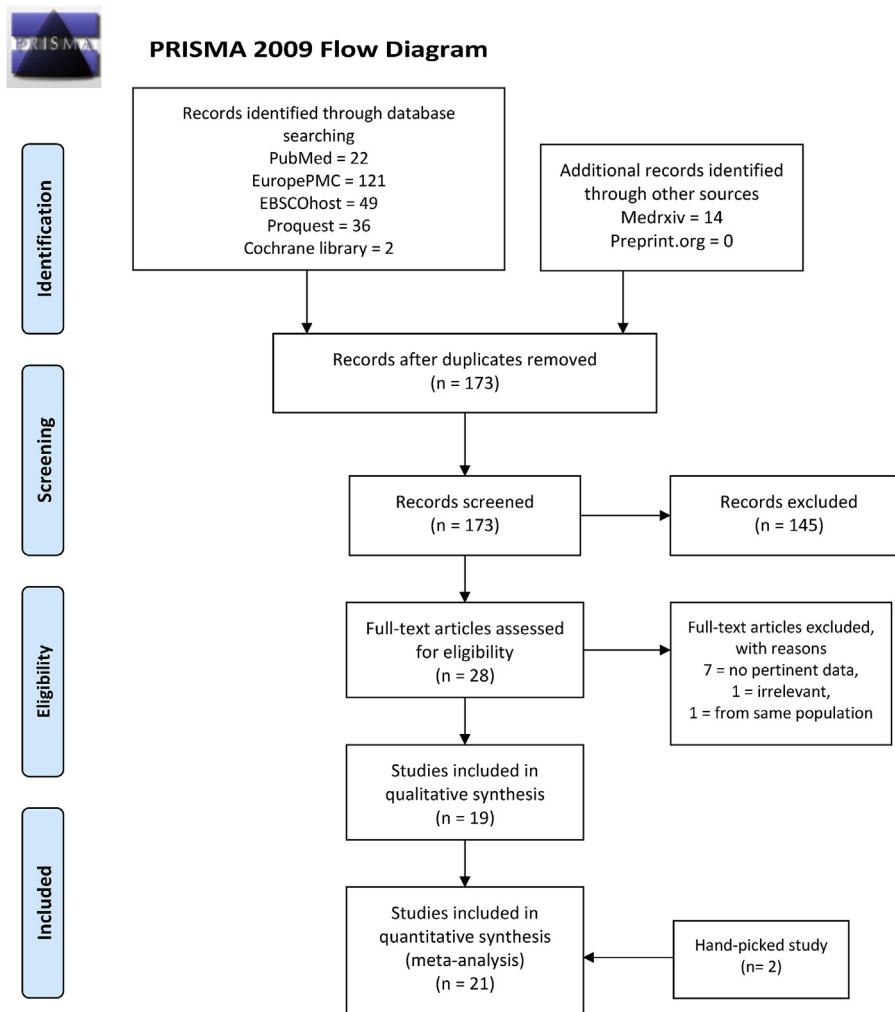


Fig. 1. Study profile.

Christensen et al. study (severity, 3–4), heterogeneity can be reduced while maintaining the significant association with a composite of poor outcomes (OR 3.19 (2.57, 3.96), $p < 0.001$; I^2 3%, $p = 0.38$).

3.7. Mean CCI score and a composite of poor outcomes

Meta-analysis showed that pooled mean CCI score was higher in the group with poor outcomes (MD 0.69 (0.20, 1.18), $p = 0.006$; I^2 94%, $p < 0.001$) (Supplementary Fig. 2). Furthermore, subgroup analysis showed that mean CCI score was significantly higher in the mortality (MD 2.03 (1.20, 2.85), $p = <0.001$; I^2 64%, $p = 0.01$) and the severe group (MD 1.05 (0.68, 1.41), $p < 0.001$; I^2 65%, $p = 0.02$). Interestingly, lower mean CCI score was associated with mechanical ventilation, albeit non-significant (MD -0.46 (-1.25, 0.35), $p = 0.27$; I^2 68%, $p = 0.01$). Additionally, the subgroup differences were significantly high [I^2 , 89.4%; $p < 0.001$]. Upon sensitivity analysis by removing Iaccarino et al. study, heterogeneity can be reduced; (MD 0.56 (0.06, 1.06), $p = 0.03$; I^2 85%, $p < 0.001$).

3.8. Publication bias & small-study effects

Funnel plot analysis showed an asymmetrical shape for mean CCI score and composite of poor outcomes (Supplementary Fig. 3). Egger's test showed no indication of small-study effects for the

CCI score 1–2 ($p = 0.734$), CCI >3 ($p = 0.544$), and a composite of poor outcomes. However, there was a statistically significant small-study effect for the mean CCI and a composite of poor outcomes analysis.

4. Discussion

This systematic review and meta-analysis showed that higher CCI was associated with increased mortality and disease severity in patients with COVID-19. The risk for mortality increases by 16% for each increase in CCI.

The maximum score for CCI is 24 (updated version) or 29 (older version). However, the studies did not provide mean/median for CCI >3, which can be anywhere between 3 and 24/29, this imprecision is a potential cause of heterogeneity as studies with higher mean CCI for the category CCI >3 may show worse prognosis.

The source of the heterogeneity in Burns et al. study, in part, is caused by employing a primary care database from System for Research In Primary Care (SIDIPAP), which did not provide detailed descriptions during hospitalization. Thus, other than age, no multivariable adjustments can be made for the HR, which might inaccurately show high HR [26].

Moreover, the high heterogeneity in per point CCI score and mortality was attributed to Price-Haywood study. This study employed adjustments with different sets of confounding variables

Table 1
Characteristic of the included studies.

No.	Author	Country	Study Design	Preprint	Subjects	Male	Overall age Mean \pm SD/Median (IQR)	Outcome	Newcastle-Ottawa Scale
1	Christensen et al.	Denmark	Retrospective cohort	No	798 vs 3265	2144/4480	55 (31)	Severe outcome	9
2	Garibaldi et al.	USA	Prospective cohort	Yes	417 vs 3265	113 vs 719	63 (26)	Mortality	9
3	Giacomelli et al.	Italy	Prospective cohort	Yes	113 vs 719	443/832	63 (26)	Severe disease and mortality	9
4	Iaccarino et al.	Italy	Prospective cohort	Yes	48 vs 185	39/48 vs 122/185	NA	Mortality	8
5	Iaccarino et al.	Italy	Cross-Sectional	No	188 vs 1403	125/188 vs 892/1403	79.6 \pm 0.8 vs 64.7 \pm 0.4	Mortality	9
6	Imam et al.	USA	Retrospective cohort	No	20 vs 1285	702/1305	61.0 \pm 16.3	Mortality	8
7	Rossi et al.	Italy	Retrospective cohort	Yes	11,205 vs 31,721	26873/42926	69 (22)	Mortality	9
8	Burn et al.	Spain	Retrospective cohort	Yes	2791 vs 15228	1669/2791 Vs 8223/15228	81 (14) vs 61 (25)	Mortality	9
9	Narain et al.	USA	Retrospective Cohort	Yes	3098	2006/3098	NA	Mortality	9
10	Price-Haywood	USA	Retrospective cohort	No	326 vs 1056	NA	NA	Mortality	9
11	Sánchez-Montalvá et al.	Spain	Prospective cohort	Yes	22 vs 60	16/22 vs 36/60	75.2 \pm 6.2 vs 53.3 \pm 19.9	Mortality	8
12	Regina et al.	Switzerland	Retrospective cohort	Yes	37 vs 163	29/37 vs 91/163	66 (22) vs 71 (27)	Mechanical ventilation	9
13	Castro et al.	USA	In silico cohort	Yes	707	213 vs 494	62.7 \pm 15.1 vs 62.2 \pm 19	Mechanical ventilation	9
14	Shashikumar	USA	Prospective cohort	Yes	10 vs 16	7/10 vs 9/16;	52.8 (23.6) vs 57.6 (36.4)	Mechanical ventilation	7
15	Chroboczek et al.	France	Retrospective cohort	Yes	59 vs 343	40/59 vs 176/343	61.5 (23) vs 65 (31)	Mechanical ventilation	7
16	Chroboczek et al.	France	Retrospective cohort	Yes	35 vs 35	27/35 vs 26/35	64 \pm 10	Intubation	9
17	Ji et al.	Korea	Retrospective case-control	Yes			58 \pm 14	Severe disease	8
18	Bhargava et al.	USA	Retrospective cohort	Yes	197	45/74 vs 58/123	63.1 (13.9) vs 59.1 (17.3)	Severe disease	9
19	Marcos et al.	Spain	Retrospective cohort (?)	Yes	918	363 vs 555	79.2 (11.5) vs 68.6 (14.7)	Severe disease	7
20	Mejía-Vilet et al.	Mexico	Prospective cohort	Yes	329	115 vs 214	53 (19) vs 49 (20)	Critical care	7
21	Balnís et al.	USA	Prospective cohort	Yes	41	13/19 vs 15/22	61.2 (27) vs 58.7 (14)	Worse outcomes	7

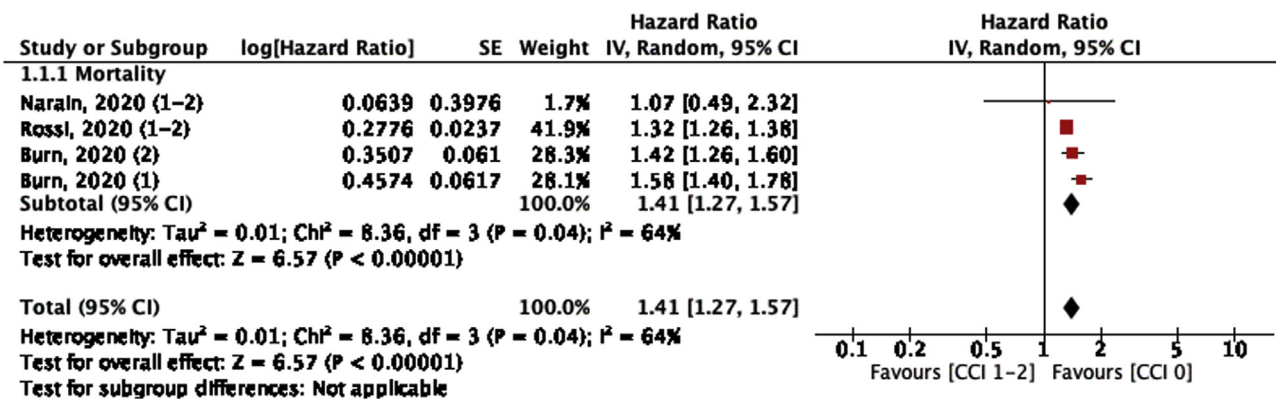


Fig. 2. The prognosis of CCI score 1–2 on mortality.

compared to other studies, which might reveal other covariates that render the HR of per point CCI score and mortality insignificant [20].

Regarding the mean Charlson score and a composite of poor outcomes, after excluding the Iaccarino study, the heterogeneity can be reduced, albeit still high. One major difference between this study and others is that the population Charlson score was clustered around the mean, reflected by the low standard deviation

[31].

The Charlson Comorbidity Index (CCI) originally was developed to predict the risk of mortality within 1 year of hospitalization. Scores are based on a number of comorbidities, each given a weighted integer from one to six depending on the severity of the morbidity [33]. It is a well-validated, simple, easy-to-apply index to evaluate patients’ prognosis and survival. During the current pandemic, the severity and mortality of COVID-19 are often

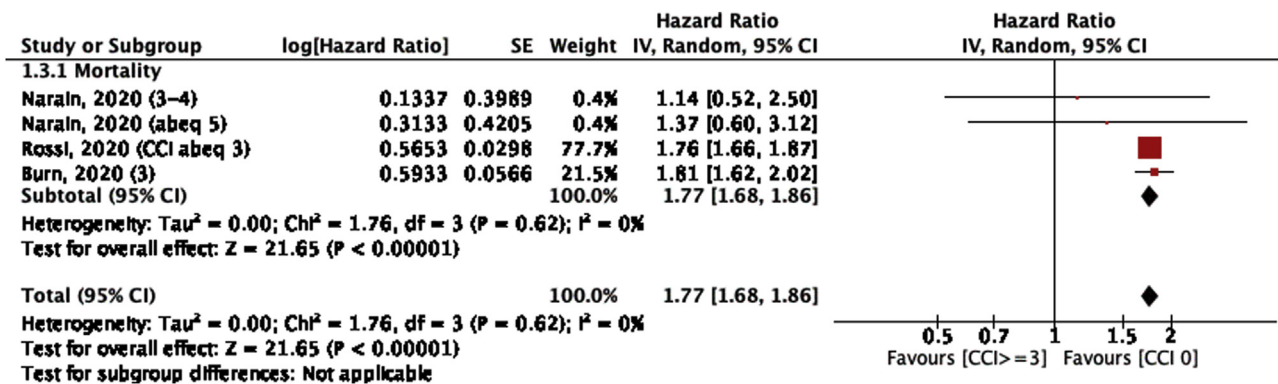


Fig. 3. The prognosis of CCI score ≥ 3 on mortality.

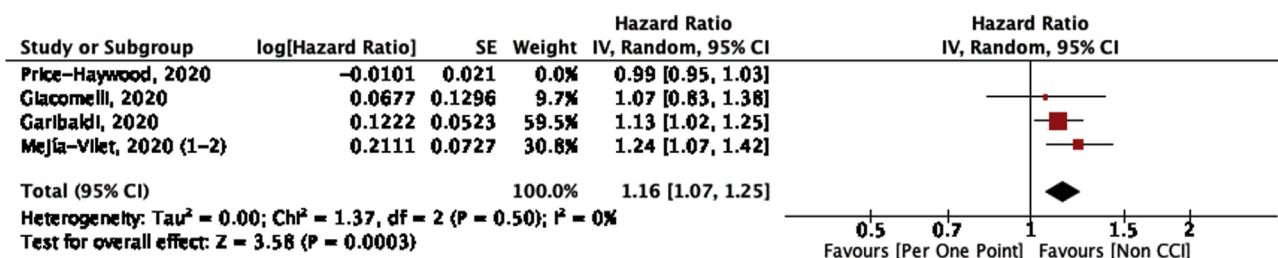


Fig. 4. Per point CCI score and mortality.

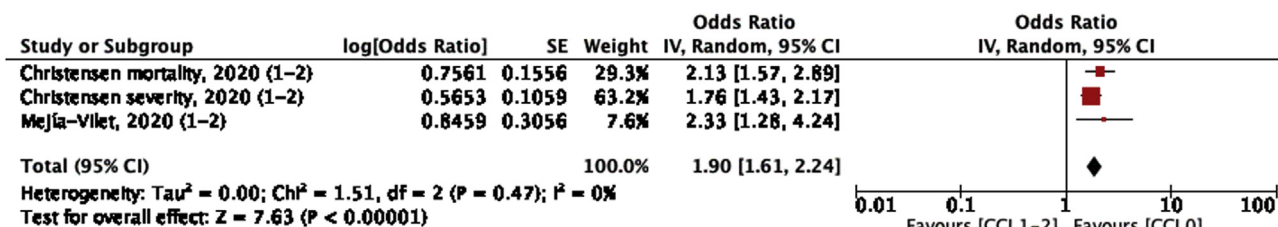


Fig. 5. The association between CCI score 1–2 and a composite of poor outcomes.

predicted by age, gender, and the presence of comorbidities, such as diabetes, cardiovascular, cerebrovascular, and respiratory diseases [34–40]. Advanced age and multiple comorbidities are independent risk factors of mortality for patients with COVID-19 [32]. The CCI score, which accumulates ages and summarizes comorbidity measures, predicts death among COVID-19 patients by an exponential increase in the odds ratio at each point of score [6,31].

Among various conditions, hypertension and diabetes mellitus are the most prevalent conditions associated with increased severity and death of COVID-19 cases [41,42]. Individuals with chronic diseases are frequently found to have overexpression of angiotensin-converting enzyme (ACE)-2 receptor. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may invade the respiratory tract or other organs by binding to the ACE2 receptor at human cells following spike protein activation by transmembrane protease serine 2 (TMPRSS2). In patients with multiple comorbidities, renin-angiotensin system (RAS) inhibitors are commonly used and it is thought that these drugs upregulate ACE2 expression which consequently facilitates the entry of SARS-CoV-2 into the targeted cells. Nonetheless, regular administration of ACE inhibitors or angiotensin receptor blockers are not associated with severity and mortality in COVID-19 and are still recommended to control blood pressure and ultimately prevent cardiovascular

complications [43]. Besides, the use of nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroid is quite prevalent in people with long-term, chronic illnesses, but it is important to remember that these drugs must be used with caution considering its side effects [44,45]. However, it is found that the use of NSAID and RAS inhibitors had no significant effect on AKI in the first 48 h or increased death, while relative immunosuppression due to steroid consumption and high prevalence of comorbidities raise concerns about the development of poor outcomes [32,46].

Various biomarkers such as C-reactive protein (CRP), D-dimer, procalcitonin, and ferritin, are often elevated in severe COVID-19 cases and evaluation of these parameters can be useful in predicting severe outcomes and complications during such pandemic [47]. Lymphopenia was also shown to be associated with higher mortality [48]. Following SARS-CoV-2 invasion, the pathogen induces hyperinflammation or cytokine release syndrome which is thought as the plausible mechanism for multiple organ dysfunction, especially acute kidney injury, acute liver injury, and coagulopathy, and the development of other serious complications in COVID-19 [49,50]. The application of CCI scoring in the context of the COVID-19 outbreak can be very useful to forecast the need for intensive care unit (ICU) admission, respiratory support, or the probability for hospital readmission. Patients with comorbidities

are often at higher risk for developing acute cardiovascular diseases, although COVID-19 in patients with comorbidity are concerning, it should not prevent or delay adequate treatment [51,52]. With the pandemic still growing worldwide, understanding the patients' clinical characteristics and risk factors that anticipate the poor outcomes in COVID-19 transmission is crucial for planning comprehensive treatment and allocating valuable resources [31].

4.1. Limitations

The included studies did not report the mean/median for CCI >3 which potentially leads to imprecision and heterogeneity. Although a pooled HR showed a 16% increased risk for every one-point increase, we cannot assess the non-linearity of the association because the studies did not fulfill the prerequisites for a non-linear dose-response analysis.

5. Conclusion

A CCI score above 0 was prognostically associated with mortality, with per point CCI score increment associated with a 16% increase of mortality risk. A CCI score above 0 also was associated with a composite of poor outcomes. Finally, a higher mean CCI score was associated with mortality and disease severity, but not mechanical ventilation. However, there was a publication bias and significant small study effect of Mean CCI score and a composite of poor outcomes, indicated by the asymmetrical shape of the inverted funnel plot analysis and by the Egger's test, respectively.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.dsx.2020.10.022>.

Authors contribution

Tuty Kuswardhani: Conceptualization, Writing – Original Draft, Project Administration. Joshua Henrina: Formal Analysis, Data Curation, Writing – Original Draft. Raymond Pranata: Formal Analysis, Writing – Review & Editing. Michael Anthonius Lim: Writing – Original Draft. Sherly Lawrensia: Data Curation, Writing – Original Draft. Ketut Suastika: Writing – Review & Editing.

Ethics approval and consent to participate

Not applicable.

Availability of data and material

Data is available upon reasonable request. All data generated or analyzed in this study are available in the respective article.

Code availability

NA.

Conflicts of interest

The authors declare that they have no competing interests.

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References

- [1] World Health Organization. Coronavirus disease (COVID-19) situation report – 131. 2020. Geneva.
- [2] Christensen DM, Strange JE, Gislason G, Torp-Pedersen C, Gerds T, Fosbøl E, et al. Charlson comorbidity index score and risk of severe outcome and death in Danish COVID-19 patients. *J Gen Intern Med* 2020. <https://doi.org/10.1007/s11606-020-05991-z>.
- [3] Guan W-J, Liang W-H, Zhao Y, Liang H-R, Chen Z-S, Li Y-M, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020;55:2000547. <https://doi.org/10.1183/13993003.00547-2020>.
- [4] Gupta R, Hussain A, Misra A. Diabetes and COVID-19: evidence, current status and unanswered research questions. *Eur J Clin Nutr* 2020. <https://doi.org/10.1038/s41430-020-0652-1>.
- [5] Gupta R, Misra A. Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infection with reference to use of therapeutic and other drugs used in Co-morbid diseases (Hypertension, diabetes etc). *Diabetes Metab Syndr Clin Res Rev* 2020;14:251–4. <https://doi.org/10.1016/j.dsx.2020.03.012>.
- [6] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987;40:373–83. [https://doi.org/10.1016/0021-9681\(87\)90171-8](https://doi.org/10.1016/0021-9681(87)90171-8).
- [7] Radovanovic D, Seifert B, Urban P, Eberli FR, Rickli H, Bertel O, et al. Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002–2012. *Heart* 2014;100:288. <https://doi.org/10.1136/heartjnl-2013-304588>. LP – 294.
- [8] Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173:676–82. <https://doi.org/10.1093/aje/kwq433>.
- [9] Hong Kong Baptist University. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range 2020.
- [10] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135. <https://doi.org/10.1186/1471-2288-14-135>.
- [11] Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018;27:1785–805. <https://doi.org/10.1177/0962280216669183>.
- [12] Stang A. Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5. <https://doi.org/10.1007/s10654-010-9491-z>.
- [13] Cochrane. Review Manager (RevMan). <https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman>; 2020.
- [14] Balnis J, Adam AP, Chopra A, Chieng HC, Feustel PJ, Overmyer KA, et al. Higher plasma levels of Chemokine CCL19 are associated with poor SARS-CoV-2 acute respiratory distress syndrome (ARDS) outcomes. *MedRxiv* 2020. <https://doi.org/10.1101/2020.05.21.20051300>. 2020.
- [15] Regina J, Papadimitriou-Oliveris M, Burger R, Filippidis P, Tschopp J, Desgranges F, et al. Epidemiology, risk factors and clinical course of SARS-CoV-2 infected patients in a Swiss university hospital: an observational retrospective study. *MedRxiv* 2020. <https://doi.org/10.1101/2020.05.11.20097741>. 2020.
- [16] Ji W, Huh K, Kang M, Hong J, Bae GH, Lee R, et al. Effect of underlying comorbidities on the infection and severity of COVID-19 in South Korea. *MedRxiv* 2020. <https://doi.org/10.1101/2020.05.08.20095174>. 2020.
- [17] Marcos M, Belhassen-Garcia M, Sanchez- Puente A, Sampedro-Gomez J, Azibeiro R, Dorado-Diaz PI, et al. Development of a severity of disease score and classification model by machine learning for hospitalized COVID-19 patients. *MedRxiv* 2020. <https://doi.org/10.1101/2020.07.13.20150177>. 2020.
- [18] Mejia-Vilet JM, Cordova-Sanchez BM, Fernandez-Camargo D, Mendez-Perez RA, Morales-Buenrostro LE, Hernandez-Gilsoul T. A risk score to predict admission to intensive care unit in patients with COVID-19: the ABC-GOALS score. *MedRxiv* 2020;5(12). <https://doi.org/10.1101/2020.05.12.20099416>. 2020.
- [19] Narain S, Stefanov D, Chau AS, Weber AG, Marder GS, Kaplan B, et al. Comparative survival analysis of immunomodulatory therapy for COVID-19 'cytokine storm': a retrospective observational cohort study. *MedRxiv* 2020. <https://doi.org/10.1101/2020.06.16.20126714>. 2020.
- [20] Price-Haywood EG, Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with Covid-19. *N Engl J Med* 2020;382:2534–43. <https://doi.org/10.1056/NEJMsa2011686>.
- [21] Giorgi Rossi P, Ferroni E, Spila Alegiani S, Leoni O, Pitter G, Cereda D, et al. Survival of hospitalized COVID-19 patients in Northern Italy: a population-based cohort study by the ITA-COVID19 Network. *MedRxiv* 2020. <https://doi.org/10.1101/2020.05.15.20103119>. 2020.
- [22] Sanchez-Montalva A, Selares-Nadal J, Espinosa-Pereiro J, Fernandez-

- Hidalgo N, Perez-Hoyos S, Salvador F, et al. Early outcomes of tocilizumab in adults hospitalized with severe COVID-19. An initial report from the Vall d'Hebron COVID-19 prospective cohort study. *MedRxiv* 2020. <https://doi.org/10.1101/2020.05.07.20094599>. 2020.
- [23] Shashikumar SP, Wardi G, Paul P, Carlile M, Brenner LN, Hibbert KA, et al. Development and prospective validation of a transparent deep learning algorithm for predicting need for mechanical ventilation. *MedRxiv. Prepr Serv. Heal Sci.* 2020. <https://doi.org/10.1101/2020.05.30.20118109>. 2020.
- [24] Vultaggio A, Vivarelli E, Virgili G, Lucenteforte E, Bartoloni A, Nozzoli C, et al. Prompt predicting of early clinical deterioration of moderate-to-severe COVID-19 patients: usefulness of a combined score using IL-6 in a preliminary study. *J. Allergy Clin. Immunol. Pract.* 2020;S2213–2198(20):30611–5. <https://doi.org/10.1016/j.jaip.2020.06.013>.
- [25] Bhargava A, Fukushima EA, Levine M, Zhao W, Tanveer F, Szpunar SM, et al. Predictors for severe COVID-19 infection. *Clin Infect Dis* 2020;19:1–7. <https://doi.org/10.1093/cid/ciaa674>.
- [26] Burn E, Tebe C, Fernandez-Bertolin S, Aragon M, Recalde M, Roel E, et al. The natural history of symptomatic COVID-19 in Catalonia, Spain: a multi-state model including 109,367 outpatient diagnoses, 18,019 hospitalisations, and 5,585 COVID-19 deaths among 5,627,520 people. *MedRxiv* 2020. <https://doi.org/10.1101/2020.07.13.20152454>. 2020.
- [27] Castro VM, Ross RA, McBride SMJ, Perlis RH. Identifying common pharmacotherapies associated with reduced COVID-19 morbidity using electronic health records. *MedRxiv* 2020. <https://doi.org/10.1101/2020.04.11.20061994>. 2020.
- [28] Chroboczek T, Lacoste M, Wackenheim C, Challan-Belval T, Amar B, Boisson T, et al. Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. *MedRxiv* 2020. <https://doi.org/10.1101/2020.05.08.20094755>. 2020.
- [29] Garibaldi BT, Fiksel J, Muschelli J, Robinson ML, Rouhizadeh M, Nagy P, et al. Patient trajectories and risk factors for severe outcomes among persons hospitalized for COVID-19 in the Maryland/DC region. *MedRxiv* 2020;5(24):20111864. <https://doi.org/10.1101/2020.05.24.20111864>. 2020.
- [30] Giacomelli A, Ridolfo AL, Milazzo L, Oreni L, Bernacchia D, Siano M, et al. 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: a prospective cohort study. *Pharmacol Res* 2020;104931. doi:10.1016/j.phrs.2020.104931.
- [31] Guido I, Guido G, Claudio B, Claudio F, Massimo S, Massimo V, et al. Age and multimorbidity predict death among COVID-19 patients. *Hypertension* 2020;76:366–72. <https://doi.org/10.1161/HYPERTENSIONAHA.120.15324>.
- [32] Imam Z, Odish F, Gill I, O'Connor D, Armstrong J, Vanood A, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. *J Intern Med* 2020. <https://doi.org/10.1111/joim.13119>.
- [33] Austin SR, Wong Y-N, Uzzo RG, Beck JR, Egleston BL. Why summary comorbidity measures such as the Charlson comorbidity index and elixhauser score work. *Med Care* 2015;53.
- [34] Pranata R, Huang I, Lim MA, Wahjoepramono EJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19 – systematic review, meta-analysis, and meta-regression. *J Stroke Cerebrovasc Dis* 2020;104949. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104949>.
- [35] Yonas E, Alwi I, Pranata R, Huang I, Lim MA, Gutierrez EJ, et al. Effect of heart failure on the outcome of COVID-19 - a meta analysis and systematic review. *Am J Emerg Med* 2020. <https://doi.org/10.1016/j.ajem.2020.07.009>.
- [36] Lim MA, Huang I, Yonas E, Vania R, Pranata R. A wave of non-communicable diseases following the COVID-19 pandemic. *Diabetes Metab Syndr Clin Res Rev* 2020;14:979–80. <https://doi.org/10.1016/j.dsx.2020.06.050>.
- [37] Pranata R, Soeroto AY, Ian H, Lim MA, Santoso P, Permana H, et al. Effect of chronic obstructive pulmonary disease and smoking on the outcome of COVID-19. *Int J Tubercul Lung Dis* 2020. <https://doi.org/10.5588/ijtld.20.0278>.
- [38] Pranata R, Lim MA, Yonas E, Vania R, Lukito AA, Siswanto BB, et al. Body mass index and outcome in patients with COVID-19: a dose-response meta-analysis. *Diabetes Metab* 2020. <https://doi.org/10.1016/j.diabet.2020.07.005>.
- [39] Lim MA, Pranata R. Coronavirus disease 2019 (COVID-19) markedly increased mortality in patients with hip fracture – a systematic review and meta-analysis. *J Clin Orthop Trauma* 2020. <https://doi.org/10.1016/j.jcot.2020.09.015>.
- [40] No Title n.d. doi:10.1016/j.dsx.2020.08.003.
- [41] Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. *J Renin-Angiotensin-Aldosterone Syst JRAAS* 2020;21. <https://doi.org/10.1177/1470320320926899.1470320320926899>.
- [42] Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – a systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr Clin Res Rev* 2020;14:395–403. <https://doi.org/10.1016/j.dsx.2020.04.018>.
- [43] Pranata R, Permana H, Huang I, Lim MA, Soetedjo NNM, Supriyadi R, et al. The use of renin angiotensin system inhibitor on mortality in patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Diabetes Metab Syndr Clin Res Rev* 2020. <https://doi.org/10.1016/j.dsx.2020.06.047>.
- [44] Lim MA, Pranata R. Worrying situation regarding the use of dexamethasone for COVID-19. *Ther Adv Respir Dis* 2020;14. <https://doi.org/10.1177/1753466620942131>.
- [45] Lim MA, Pranata R. The insidious threat of jamu and unregulated traditional medicines in the COVID-19 era. *Diabetes Metab Syndr Clin Res Rev* 2020. <https://doi.org/10.1016/j.dsx.2020.06.022>.
- [46] Valeri AM, Robbins-Juarez SY, Stevens JS, Ahn W, Rao MK, Radhakrishnan J, et al. Presentation and outcomes of patients with ESKD and COVID-19. *J Am Soc Nephrol* 2020;31:1409. <https://doi.org/10.1681/ASN.2020040470>. LP – 1415.
- [47] Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Ther Adv Respir Dis* 2020;14. <https://doi.org/10.1177/1753466620937175>.
- [48] Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. *J Intensive Care* 2020;8. <https://doi.org/10.1186/s40560-020-00453-4>.
- [49] Lim MA, Pranata R, Huang I, Yonas E, Soeroto AY, Supriyadi R. Multiorgan failure with emphasis on acute kidney injury and severity of COVID-19: systematic review and meta-analysis. *Can J Kidney Heal Dis* 2020;7. <https://doi.org/10.1177/2054358120938573>.
- [50] Pranata R, Supriyadi R, Huang I, Permana H, Lim MA, Yonas E, et al. The association between chronic kidney disease and new onset renal replacement therapy on the outcome of COVID-19 patients: a meta-analysis. *Clin Med Insights Circulatory, Respir Pulm Med* 2020;14. <https://doi.org/10.1177/1179548420959165>.
- [51] July J, Pranata R. Impact of the coronavirus disease pandemic on the number of strokes and mechanical thrombectomies: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* 2020;29. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105185>.
- [52] Pranata R, Lim MA, Yonas E, Siswanto BB, Meyer M. Out-of-hospital cardiac arrest prognosis during the COVID-19 pandemic. *Intern Emerg Med* 2020;15. <https://doi.org/10.1007/s11739-020-02428-7>.