



ORIGINAL PAPER

Dyslipidaemia and mortality in COVID-19 patients: a meta-analysis

M. Zuin¹, G. Rigatelli², C. Bilato ³, C. Cervellati¹, G. Zuliani¹ and L. Roncon ²

From the ¹Department of Translational Medicine, University of Ferrara, Ferrara, Italy, ²Department of Cardiology, Santa Maria della Misericordia Hospital, Rovigo, Italy and ³Department of Cardiology, West Vicenza General Hospitals, Arzignano, Vicenza, Italy

Address correspondence to Prof L. Roncon, Department of Cardiology, Santa Maria della Misericordia Hospital, Rovigo General Hospital, Viale tre Martiri, Rovigo 45100, Italy. email: lorisoncon@gmail.com

Summary

Background: The prevalence and prognostic implications of pre-existing dyslipidaemia in patients infected by the SARS-CoV-2 remain unclear.

Aim: To assess the prevalence and mortality risk in COVID-19 patients with pre-existing dyslipidaemia.

Design: Systematic review and meta-analysis.

Methods: Preferred reporting items for systematic reviews and meta-analyses guidelines were followed in abstracting data and assessing validity. We searched MEDLINE and Scopus to locate all the articles published up to 31 January 2021, reporting data on dyslipidaemia among COVID-19 survivors and non-survivors. The pooled prevalence of dyslipidaemia was calculated using a random-effects model and presenting the related 95% confidence interval (CI), while the mortality risk was estimated using the Mantel-Haenszel random-effect models with odds ratio (OR) and related 95% CI. Statistical heterogeneity was measured using the Higgins I² statistic.

Results: Of about 18 studies, enrolling 74 132 COVID-19 patients (mean age 70.6 years), met the inclusion criteria and were included in the final analysis. The pooled prevalence of dyslipidaemia was 17.5% of cases (95% CI: 12.3–24.3%, $P < 0.0001$), with high heterogeneity ($I^2 = 98.7\%$). Pre-existing dyslipidaemia was significantly associated with higher risk of short-term death (OR: 1.69, 95% CI: 1.19–2.41, $P = 0.003$), with high heterogeneity ($I^2 = 88.7\%$). Due to publication bias, according to the Trim-and-Fill method, the corrected random-effect ORs resulted 1.61, 95% CI 1.13–2.28, $P < 0.0001$ (one studies trimmed).

Conclusion: Dyslipidaemia represents a major comorbidity in about 18% of COVID-19 patients but it is associated with a 60% increase of short-term mortality risk.

Introduction

Several analyses have demonstrated that clinical outcomes in patients with SARS-CoV-2 infection are closely related to the burden of associated comorbidities,¹ such as arterial hypertension

(HT), diabetes mellitus (DM) and cardiovascular disease (CVDs).^{2–4}

It is, therefore, crucial to identify which pre-existing comorbidities can influence the survival of COVID-19 patients to promote the adoption of closer monitoring and more aggressive

Received: 26 March 2021; Revised (in revised form): 29 March 2021

© The Author(s) 2020. Published by Oxford University Press on behalf of the Association of Physicians. All rights reserved.

For permissions, please email: journals.permissions@oup.com

treatments. Recent analyses have investigated the potential beneficial effect of statin therapy on the short-term mortality,^{5,6} but a comprehensive assessment of data regarding the prognostic role of dyslipidaemia in SARS-CoV-2 infected individuals has not yet been performed. The aim of this study is to estimate the pooled prevalence and the influence of dyslipidaemia on short-term mortality in COVID-19 patients by a systematic review and meta-analysis of the available data.

Materials and methods

Data sources and searches

The study was performed in accordance with the Preferred Report Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary File S1).⁷ PubMed and Scopus databases were systematically searched for articles, published in English language, from inception through 31 January 2021 with the following Medical Subject Heading (MESH) terms: COVID-19 [Title/Abstract] OR SARS-CoV-2 [Title/Abstract] AND 'Survivors' [Title/Abstract]. In addition, references from the included studies were screened to potentially identify other investigations meeting the inclusion criteria.

Study selection

Specifically, inclusion criteria were: (i) studies enrolling subjects with a confirmed diagnosis of COVID-19 and (ii) studies providing data on the prevalence of dyslipidaemia/hyperlipidaemia between survivors (S) and non-survivors (NS). Conversely, case reports, review articles, abstracts, editorials/letters and case series with <10 participants were excluded. Each included article was independently evaluated by two reviewers (M.Z. and L.R.); in case of discrepancies a third author was involved, and final consensus was achieved through discussion.

Data extraction and quality assessment

Data were independently extracted by two reviewers (M.Z. and G.R.) using a standardized protocol. Disagreements were resolved. For this meta-analysis, the following data elements were extracted: sample size, number of survivors (S) and NS, mean age, gender and major comorbidities (HT and DM) stratified according to the outcome status (S and NS). The quality of included studies was graded using the Newcastle–Ottawa quality assessment scale (NOS).⁸

Outcomes

The prevalence of dyslipidaemia in COVID-19 patients was chosen as the primary outcome while its associated mortality risk was selected as the secondary outcome.

Data synthesis and analysis

Continuous variables were expressed as mean \pm standard deviation (SD) or as median with corresponding interquartile range (IQR) while categorical variables as counts and percentages. The cumulative prevalence of dyslipidaemia (n/N), defined as the ratio between patients with pre-existing dyslipidaemia (n) and the number of patients enrolled in each study (N), were pooled using a random-effects model and presented with the corresponding 95% confidence interval (CI). To estimate the mortality risk, data were pooled using the Mantel–Haenszel random-

effect models with odds ratio (OR) as the effect measure with 95% CI. Heterogeneity among studies was assessed using Higgins and Thomson I^2 statistic where I^2 values corresponding with the following levels of heterogeneity: low (<25%), moderate (25–75%) and high (>75%).⁹ Considering that funnel plots have intrinsic limitations in detecting publication bias, we further carried out the Egger's regression test.¹⁰ In case of publication bias, the Duval and Tweedie trim-and-fill method was applied. To further appraise the impact of potential baseline confounders, a meta-regression analysis was performed. The following variables were considered: age, body mass index, gender, DM, arterial HT, chronic kidney disease, coronary artery disease, cerebrovascular events and heart failure (HF). All meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, USA).

Results

Search results

A total of 2357 articles were obtained by our search strategy. After excluding duplicates and preliminary screening, 545 full-text articles were assessed for eligibility and 527 studies were excluded for not meeting the inclusion criteria, leaving 18 investigations fulfilling the inclusion criteria.^{11–28} A flow diagram of the literature search and related screening process is shown in Figure 1.

Study characteristics

Overall, 74 132 COVID-19 patients (mean age 70.6 years) were included in the analysis. The general characteristics of the included studies are summarized in Table 1. The mortality rate was 12.0% (95% CI 11.4–12.7). Overall, NS were older, hypertensive and diabetic compared to S. Quality assessment showed that all the studies were of moderate-high quality according to the NOS scale.

Pooled prevalence of dyslipidaemia

The prevalence of dyslipidaemia among COVID-19 patients ranged between 0.8% and 68.8%. A random-effect model revealed a pooled prevalence of dyslipidaemia in 17.5% of cases (95% CI: 12.3–24.3%, $P < 0.0001$). A high heterogeneity was observed in the analysis ($I^2 = 98.7%$) (Figure 2A). The relative funnel plot is presented in Figure 3A. The Egger's test did not show publication bias ($t = 1.355$; $P = 0.194$).

Dyslipidaemia and mortality risk

On pooled analysis, pre-existing dyslipidaemia was significantly associated with a higher risk of death in the short-term period (OR: 1.69, 95% CI: 1.19–2.41, $P = 0.003$) (Figure 2B). Again, heterogeneity was high ($I^2 = 88.7%$). Visual inspection of the relative funnel plot (Figure 3B) evidenced publication bias, confirmed by the Egger's test, as well ($t = 3.336$, $P = 0.004$). According to the Trim-and-Fill method, the corrected random-effect ORs was 1.61 (95% CI 1.13–2.28, $P < 0.0001$) (one studies trimmed).

Meta-regression

Meta-regression analysis revealed a direct relationship between short-term mortality and DM ($P = 0.005$, coefficient: -0.046 , 95% CI -0.083 to -0.014), HT ($P = 0.0001$; coefficient -0.051 ; 95% CI -0.077 – -0.025) and HF ($P = 0.001$, coefficient 0.043 , 95% CI 0.017 –

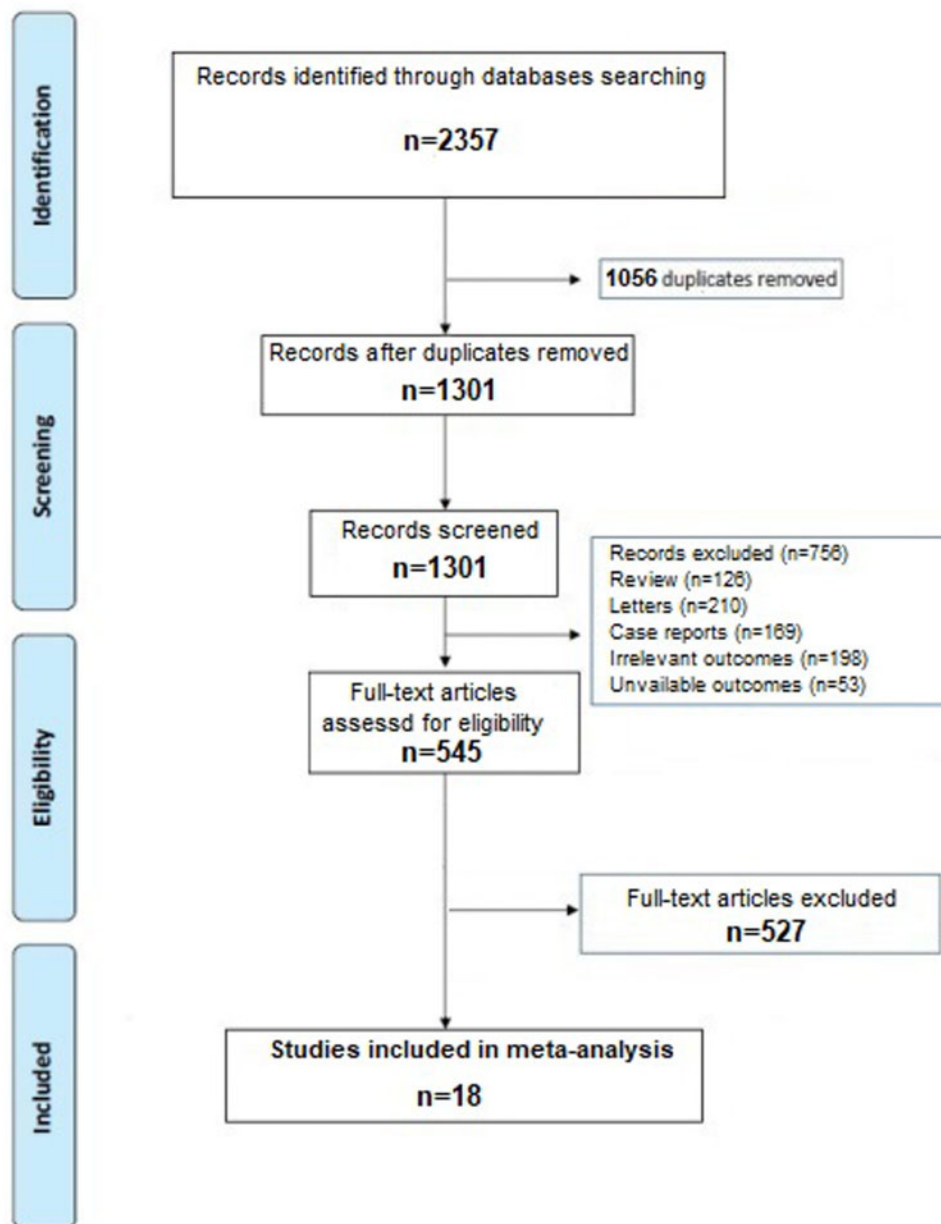


Figure 1. PRISMA flow diagram.

0.070). Conversely, no association was found considering age, body mass index, male gender, chronic kidney disease, coronary artery disused and cerebrovascular events (Table 2).

Discussion

Three major findings emerge from the present meta-analysis based on more 70 000 patients. Firstly, dyslipidaemia is present in <1 out of 4 COVID-19 patients. Secondly, and more importantly, SARS-CoV-2 infected patients with a pre-existing dyslipidaemia had an approximately 70% higher risk of death in the short-term period. Thirdly, this last one association was influenced by HT, DM and HF.

Present results reinforce the concept that comorbidities play a pivotal role in determining the COVID-19 patient's outcome. Given the large number of subjects analysed, our analysis

provides additional information on the results of individual studies, extrapolating the results of the general population with history of dyslipidaemia and COVID-19 infection. As previously demonstrated, HT, DM and CVDs have been related to a worst outcome in the short-term period.²⁻⁴ Furthermore, also HF has resulted to influence the outcome of infected patients.^{29,30} According to our observations, also dyslipidaemia is closely related to a SARS-Cov-2 worse prognosis, besides being a major cardiovascular risk factors and frequently associated with the clinical conditions mentioned above. Investigations on the prognostic role of dyslipidaemia in COVID-19 patients are scant since previous investigations have mainly focused on the modification of the lipid profile occurring during the disease. To this regard, a recent analysis has suggested that lipids, especially cholesterol, may play an important role in viral replication, internalization and immune activation in COVID-19 patients.³¹ By

Table 1. Characteristics of studies included in the meta-analysis

| Author | Sample size | NS | S | Age (years) [IQR]; (SD) | | Males N, (%) | | DM N, (%) | | HT N, (%) | | NOS |
|------------------------|-------------|------|-------|-------------------------|-----------------------------|----------------|------------------------------|----------------|------------------------------|----------------|------------------------------|-----|
| | | | | NS | S | NS | S | NS | S | NS | S | |
| Cipriani et al. | 109 | 20 | 89 | 86 [77–87] | 69 ^b [57–79] | 10 (50) | 60 (71) | 6 (30) | 21 (24) | 16 (80) | 52 (58) | 8 |
| Ferrando et al. | 663 | 203 | 460 | 68 [62–73] | 65 [53–71] | 47 (72.3) | 310 (67.6) | 61 (30.5) | 90 (19.7) ^a | 115 (54.6) | 214 (46.5) ^a | 8 |
| Gayam et al. | 408 | 132 | 276 | 71 [62–80] | 63 ^b [53–73] | 76 (32.9) | 155 ^b (67.1) | 72 (40.9) | 104 ^b (59) | 105 (38.7) | 166 ^b (61.2) | 8 |
| Huang et al. | 2623 | 232 | 2391 | 64 [49–73] | 70 [63–78] | 71 (30.6) | 1229 ^b (46.8) | NR | | NR | | 7 |
| Kocayigit et al. | 169 | 30 | 139 | 73.2 (10.5) | 64.2 (11.4) | 15 (50.0) | 64 (37.8) | 13 (43.3) | 46 (33.1) | NR | | 8 |
| Quisi et al. | 349 | 38 | 311 | 69 [60–76] | 55 ^b [41–61] | 14 (36.8) | 13.9 (44.7) | 13 (34.2) | 93 (23.9) | 20 (52.1) | 101 ^a (32.5) | 8 |
| Yan et al. | 1004 | 40 | 964 | 68 [58–79] | 62 ^a [50–70] | 27 (67.5) | 466 ^a (48.3) | 10 (25.0) | 97 ^a (10.1) | 20 (50.0) | 215 ^b (22.3) | 8 |
| Mendes et al. | 235 | 76 | 159 | 86.9 (6.4) | 86.0 (6.5) | 48 (63.1) | 54 ^b (33.9) | 23 (30.3) | 31 ^a (19.5) | 56 (73.7) | 112 (70.4) | 8 |
| Chang et al. | 106 | 30 | 76 | 75.5 (9.3) | 65 ^b (16.3) | 19 (63.0) | 35 (46.1) | 17 (56.7) | 25 ^a (32.9) | 20 (66.7) | 39 (51.3) | 7 |
| Sun et al. | 50 | 15 | 35 | 69 [61–80] | 73 [63–78] | 8 (53.3) | 26 (76.2) | 7 (46.7) | 16 (45.7) | 9 (60.0) | 19 (54.2) | 8 |
| Cantenys-Molina et al. | 702 | 112 | 590 | 79 (72–84) | 61 ^b (48–72) | 71 (63.9) | 334 (56.6) | 49 (43.8) | 175 ^a (29.7) | 81 (73.4) | 224 ^b (37.9) | 8 |
| Rosenthal et al. | 64781 | 7355 | 57426 | 74.2 (13.4) | 53.7 ^b (19.3) | 4267 (58.0) | 27701 ^b (48.2) | 3616 (49.1) | 18091 ^b (31.5) | 5860 (79.7) | 24376 ^b (42.4) | 8 |
| Almazeedi et al. | 1096 | 19 | 1077 | 55 (10.1) | 38.7 ^b (15.1) | 16 (84.2) | 872 ^b (80.9) | 6 (31.5) | 149 ^b (13.8) | 8 (50.0) | 169 ^b (15.6) | 7 |
| Gomez-Antuner et al. | 746 | 286 | 460 | 79 [74–86] | 75 ^b [66–82] | 247 (86.7) | 365 ^a (79.4) | 72 (25.4) | 119 (26.1) | 215 (75.7) | 298 ^b (65.0) | 8 |
| Rossi et al. | 590 | 256 | 334 | 79.5 [74–84] | 72.9 [64–80] | 187 (73.0) | 212 ^a (63.5) | 67 (26.2) | 70 (21.0) | NR | | 8 |
| Cho et al. | 143 | 36 | 107 | 75.8 (16.8) | 68.5 (17.2) | 20 (55.6) | 68 (63.6) | 9 (25.0) | 41 (38.3) | 16 (44.4) | 63 (58.9) | 8 |
| Lanza et al. | 324 | 44 | 280 | 77.8 (9.0) | 64.1 ^b (15.0) | 34 (77.3) | 180 (64.3) | 5 (11.4) | 32 (11.4) | 36 (81.8) | 133 (47.5) | 8 |
| Saifi et al. | 34 | 16 | 18 | 93 [90–99] | 93 [90–101] | 9 (50.0) | 8 (50.0) | 2 (11.1) | 3 (18.8) | 15 (83.3) | 13 (81.3) | 7 |

DM, diabetes mellitus; HT, arterial hypertension; IQR: interquartile range; NOS, Newcastle–Ottawa quality assessment scale; NS: non-survivors; S: survivors; SD: standard deviation.

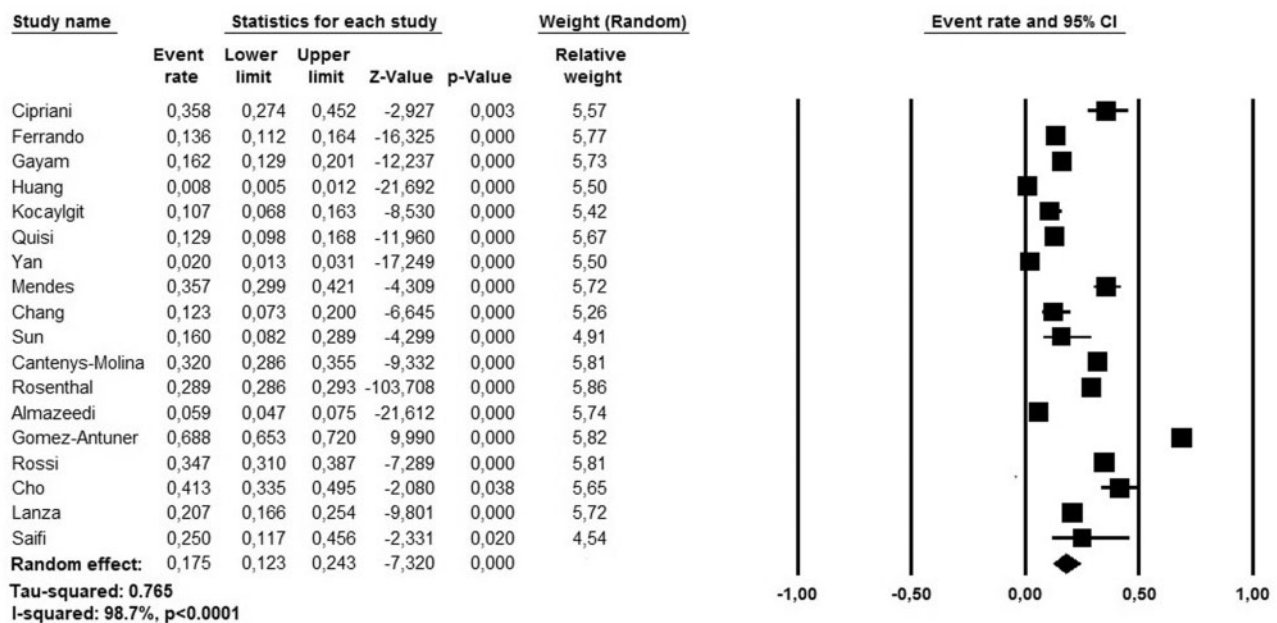
^aP < 0.05 between NSs and survivors and ^bP < 0.001 between NSs and survivors.

contrast, Qin et al. reported that total (TC) and low-density lipoprotein cholesterol (LDL-C) levels at admission negatively correlated with in-hospital stay, suggesting that the gradual increase of TC and LDL-C indicate the progressive recovery of the patients with SARS-CoV-2 infection.³² Similarly, Sun et al. observed that low apolipoprotein A-1 and high-density lipoprotein cholesterol (HDL-C) levels predicted the severity of the SARS-CoV-2 infection and the poor outcome.³¹ Conversely, to the best of our knowledge, this study represents the first meta-analysis examining the prognostic significance of dyslipidaemia which pre-exists the SARS-CoV-2 infection, eliminating the possibility that the lipid profile was already altered at the beginning of the disease, similarly to what already observed in patients with other infections or sepsis.^{20,33–36}

Lipids might play an important role in the pathophysiology of SARS-CoV-2 infection. The efficiency of viral infection is significantly reduced when cholesterol is deficient in the cell

membrane.³⁷ Moreover, when the viral infection has already occurred, increased levels of LDL-C may promote inflammatory activation and increased secretion of proinflammatory cytokines while lower HDL-C levels may trigger the dysregulation of the innate immune response.³⁸ In the meanwhile, LDL-C or triglyceride accumulation led to endothelial dysfunction, increasing the risk of cardiovascular complications or acute events which, in turn, may be responsible of poorer outcomes.³⁹ These theories need to be confirmed in larger studies. However, beyond the dynamic changes of lipid profile during COVID-19 infection, our results may be useful in both clinical practice and prevention strategies. Indeed, hospitalized COVID-19 patients with history of dyslipidaemia might require a more aggressive therapeutic strategies since the beginning of the disease to reduce their mortality risk. Moreover, dyslipidaemic patients might benefit from an earlier anti SARS-CoV-2 immunization, considering their higher risk of poor outcome if infected. To this

A



B

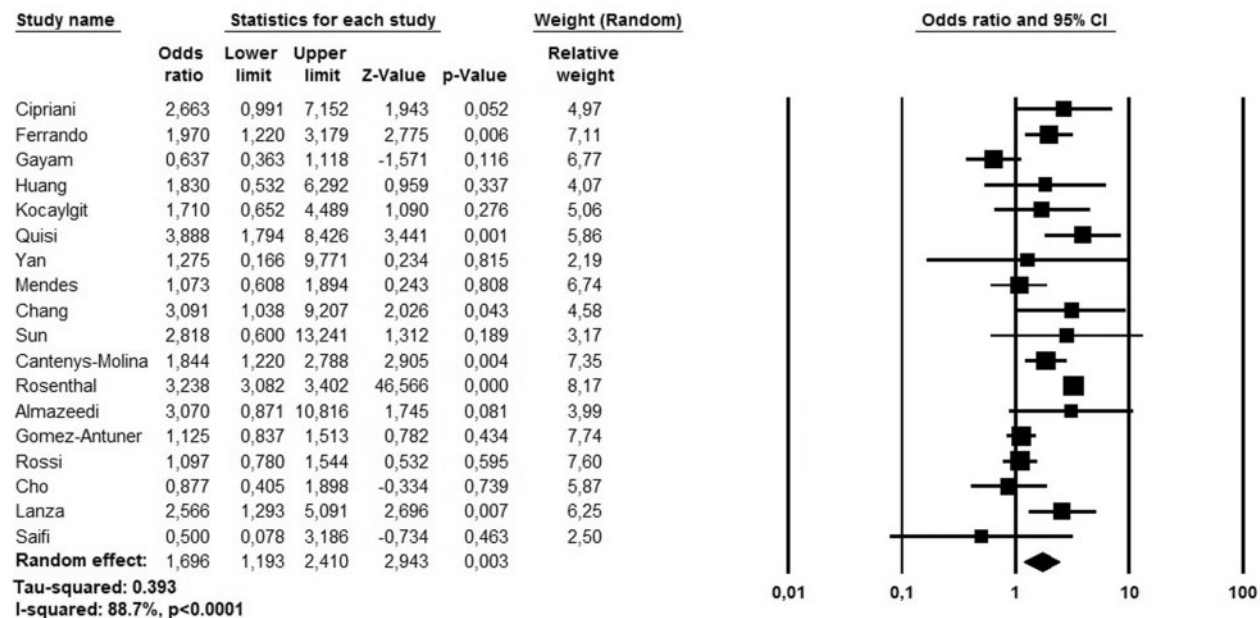


Figure 2. (A) Pooled prevalence of pre-existing dyslipidaemia in COVID-19 patients. (B) Forest plot investigating the mortality risk due pre-existing dyslipidaemia in COVID-19 patients using a random-effect model.

regard, our findings reinforce the concept that the accurate identification of the unfavourable prognostic factors is essential in helping clinicians and policy makers in tailoring the management strategies for COVID-19 patients.

This analysis is based on a generic definition of dyslipidaemia, which encompasses distinctive clinical phenotypes with different prognostic significance; on the other hand, our methodological approach reduces the potential biases of the

quantitative lipid profile evaluation which, as previously mentioned, may be already impaired in the beginning subclinical phase of the infection.^{20,31,32}

Limitations

We recognize some limitations to our study, such as the observational and retrospective nature of the reviewed studies and

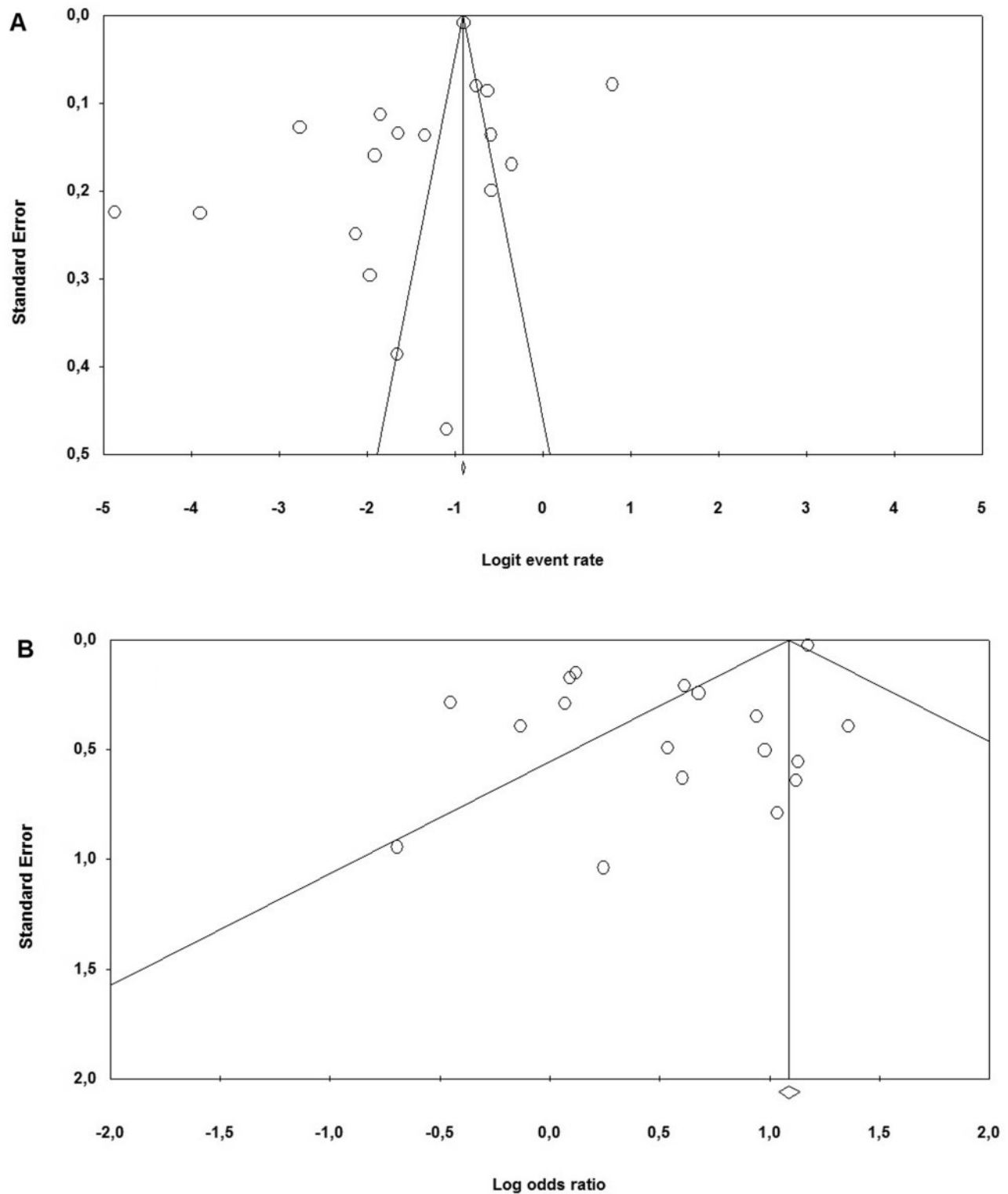


Figure 3. Funnel plots for (A) the pooled prevalence of dyslipidaemia in COVID-19 patients and (B) for the mortality risk due to dyslipidaemia in COVID-19 patients.

their intrinsic and inherited biases. Furthermore, the potential underestimation of pre-existing dyslipidaemia in the hospitalized patients and the observed high heterogeneity, which probably depends on the participants' inclusion criteria as well as on

the study designs, may have resulted in conclusions. Finally, we cannot evaluate the impact of different treatment strategies on the relationship between pre-existing dyslipidaemia and short-term mortality.

Table 2. Meta-regression analysis of the effects of presenting features on short-term mortality

| Variable | Number of studies | Coefficient | SE | 95% CI | | P-value |
|----------------|-------------------|-------------|-------|--------|-------|---------|
| | | | | Lower | Upper | |
| Age | 18 | -0.033 | 0.024 | -0.081 | 0.014 | 0.167 |
| BMI | 7 | 0.006 | 0.232 | -0.449 | 0.462 | 0.976 |
| Gender (Males) | 18 | -0.020 | 0.030 | 0.080 | 0.039 | 0.499 |
| DM | 17 | 0.049 | 0.017 | 0.014 | 0.083 | 0.005 |
| HT | 15 | 0.051 | 0.013 | 0.025 | 0.077 | 0.0001 |
| CKD | 12 | -0.030 | 0.030 | -0.090 | 0.029 | 0.313 |
| CAD | 11 | -0.055 | 0.060 | -0.174 | 0.063 | 0.358 |
| CVE | 12 | 0.001 | 0.058 | -0.112 | 0.114 | 0.984 |
| HF | 11 | 0.043 | 0.013 | 0.017 | 0.070 | 0.001 |

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CVE, cerebrovascular events; DM, diabetes mellitus; HF, heart failure; HT, arterial hypertension; SE, standard error.

Conclusion

Dyslipidaemia is associated with an increased risk of short-term mortality in COVID-19 patients, influenced by HT, DM and HF. Present results reinforce the concept that cardiovascular comorbidities and risk factors play a pivotal role in determining the COVID-19 patient's outcome.

Supplementary material

Supplementary material is available at QJMED online.

Funding

None.

Conflict of interest. None of the authors have conflicts of interest to declare.

References

- De Giorgi A, Fabbian F, Greco S, Di SE, De GR, Passaro A, et al. Prediction of in-hospital mortality of patients with SARS-CoV-2 infection by comorbidity indexes: an Italian internal medicine single center study. *Eur Rev Med Pharmacol Sci* 2020; **24**:10258–66.
- Zuin M, Rigatelli G, Zuliani G, Rigatelli A, Mazza A, Roncon L. Arterial hypertension and risk of death in patients with COVID-19 infection: systematic review and meta-analysis. *J Infect* 2020; **81**:e84–6.
- Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. *J Clin Virol* 2020; **127**:104354.
- Bae S, Kim SR, Kim MN, Shim WJ, Park SM. Impact of cardiovascular disease and risk factors on fatal outcomes in patients with COVID-19 according to age: a systematic review and meta-analysis. *Heart* 2021; **107**:373–80.
- Pal R, Banerjee M, Yadav U, Bhattacharjee S. Statin use and clinical outcomes in patients with COVID-19: an updated systematic review and meta-analysis. *Postgrad Med J* 2021, in press. doi: 10.1136/postgradmedj-2020-139172.
- Peymani P, Dehesh T, Aligolighasemabadi F, Sadeghdoust M, Kotfis K, Ahmadi M, et al. Statins in patients with COVID-19: a retrospective cohort study in Iranian COVID-19 patients. *Transl Med Commun* 2021; **6**:3.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**:e1000097.
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. 2012; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (4 February 2020, date last accessed).
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**:557–60.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–34.
- Cipriani A, Capone F, Donato F, Molinari L, Ceccato D, Saller A, et al. Cardiac injury and mortality in patients with Coronavirus disease 2019 (COVID-19): insights from a mediation analysis. *Intern Emerg Med* 2021; **16**:419.
- Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Bordell A, et al. Patient characteristics, clinical course and factors associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: a prospective, cohort, multicentre study. *Rev Esp Anestesiol Reanim* 2020; **67**: 425–437.
- Gayam V, Chobufo MD, Merghani MA, Lamichhane S, Garlapati PR, Adler MK. Clinical characteristics and predictors of mortality in African-Americans with COVID-19 from an inner-city community teaching hospital in New York. *J Med Virol* 2021; **93**:812–819.
- Huang W, Li C, Wang Z, Wang H, Zhou N, Jiang J, et al. Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases. *Sci China Life Sci* 2020; **63**:1678–87.
- Kocayigit I, Kocayigit H, Yaylaci S, Can Y, Erdem AF, Karabay O. Impact of antihypertensive agents on clinical course and in-hospital mortality: analysis of 169 hypertensive patients hospitalized for COVID-19. *Rev Assoc Med Bras (1992)* 2020; **66**:71–6.
- Quisi A, Alici G, Harbahoğlu H, Genç Ö, Er F, Allahverdiyev S, et al. The CHA2DS2-VASc score and in-hospital mortality in patients with COVID-19: a multicenter retrospective cohort study. *Turk Kardiyol Dern Ars* 2020; **48**:656–63.
- Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: a retrospective cross-sectional study. *J Med Virol* 2020; **92**:2573–81.
- Mendes A, Serratrice C, Herrmann FR, Genton L, Pérvier S, Scheffler M, et al. Predictors of in-hospital mortality in older

- patients with COVID-19: the COVID age study. *J Am Med Dir Assoc* 2020; **21**:1546–54.e3.
19. Chang MC, Hwang JM, Jeon JH, Kwak SG, Park D, Moon JS. Fasting plasma glucose level independently predicts the mortality of patients with Coronavirus Disease 2019 Infection: a multicenter, Retrospective Cohort Study. *Endocrinol Metab (Seoul)* 2020; **35**:595–601.
 20. Sun JT, Chen Z, Nie P, Ge H, Shen L, Yang F, et al. Lipid profile features and their associations with disease severity and mortality in patients with COVID-19. *Front Cardiovasc Med* 2020; **7**: 584987.
 21. Cantenys-Molina S, Fernández-Cruz E, Francos P, Lopez Bernaldo de Quirós JC, Muñoz P, Gil-Herrera J. Lymphocyte subsets early predict mortality in a large series of hospitalized COVID-19 patients in Spain. *Clin Exp Immunol* 2021; **203**: 424–432; doi: 10.1111/cei.13547.
 22. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with in-hospital mortality in a US National sample of patients with COVID-19. *JAMA Netw Open* 2020; **3**: e2029058.
 23. Almazeedi S, Al-Youha S, Jamal MH, Al-Haddad M, Al-Muhaini A, Al-Ghimlas F, et al. Characteristics, risk factors and outcomes among the first consecutive 1096 patients diagnosed with COVID-19 in Kuwait. *E Clin Med* 2020; **24**:100448.
 24. Gómez Antúnez M, Muiño Míguez A, Bendala Estrada AD, Maestro de la Calle G, Monge Monge D, Boixeda R, et al. Clinical characteristics and prognosis of COPD patients hospitalized with SARS-CoV-2. *Int J Chron Obstruct Pulmon Dis* 2021; **15**:3433–45.
 25. Rossi L, Malagoli A, Biagi A, Zanni A, Sticozzi C, Comastri G, et al. Renin-angiotensin system inhibitors and mortality in patients with COVID-19. *Infection* 2021; **49**:287–94.
 26. Cho JH, Namazi A, Shelton R, Ramireddy A, Ehdaie A, Shehata M, et al. Cardiac arrhythmias in hospitalized patients with COVID-19: a prospective observational study in the western United States. *PLoS One* 2020; **15**:e0244533.
 27. Lanza GA, De Vita A, Ravenna SE, D’Aiello A, Covino M, Franceschi F, et al. Electrocardiographic findings at presentation and clinical outcome in patients with SARS-CoV-2 infection. *Europace* 2021; **23**:123–129; doi: 10.1093/europace/eaab245.
 28. Saifi ES, Giorgi-Pierfranceschi M, Salvetti M, Maninetti L, Cavalli I, Muiesan ML. Factors associated with survival in older patients affected by COVID-19: a retrospective cohort study. *Arch Gerontol Geriatr* 2021; **94**:104349.
 29. Chatrath N, Kaza N, Pabari PA, Fox K, Mayet J, Barton C, et al. The effect of concomitant COVID-19 infection on outcomes in patients hospitalized with heart failure. *ESC Heart Fail* 2020; **7**: 4443–7.
 30. Alvarez-Garcia J, Lee S, Gupta A, Cagliostro M, Joshi AA, Rivas-Lasarte M, et al. Prognostic impact of prior heart failure in patients hospitalized with COVID-19. *J Am Coll Cardiol* 2020; **76**:2334–48.
 31. Roccaforte V, Daves M, Lippi G, Spreafico M, Bonato C. Altered lipid profile in patients with COVID-19 infection. *J Lab Prec Med* 2021; **6**:2.
 32. Qin C, Minghan H, Ziwen Z, Yukun L. Alteration of lipid profile and value of lipids in the prediction of the length of hospital stay in COVID-19 pneumonia patients. *Food Sci Nutr* 2020; **8**: 6144–52.
 33. Wang X, Nijman R, Camuzeaux S, Sands C, Jackson H, Kaforou M, et al., EUCLIDS Consortium. Plasma lipid profiles discriminate bacterial from viral infection in febrile children. *Sci Rep* 2019; **9**:17714.
 34. Heaton NS, Randall G. Multifaceted roles for lipids in viral infection. *Trends Microbiol* 2011; **19**:368–75.
 35. Golucci APBS, Marson FAL, Ribeiro AF, Nogueira RJN. Lipid profile associated with the systemic inflammatory response syndrome and sepsis in critically ill patients. *Nutrition* 2018; **55–56**:7–14.
 36. Mecatti GC, Messias MCF, de Oliveira Carvalho P. Lipidomic profile and candidate biomarkers in septic patients. *Lipids Health Dis* 2020; **19**:68.
 37. Ren X, Glende J, Yin J, Schwegmann-Wessels C, Herrler G. Importance of cholesterol for infection of cells by transmissible gastroenteritis virus. *Virus Res* 2008; **137**:220–4.
 38. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. *Nat Rev Immunol* 2015; **15**:104–16.
 39. Choi GJ, Kim HM, Kang H. The potential role of dyslipidemia in COVID-19 severity: an umbrella review of systematic reviews. *J Lipid Atheroscler* 2020; **9**:435–48.