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

Running Head: Dyslipidaemia and mortality in COVID-19 patients

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Type of manuscript: Meta-analysis

Word count: 1659

Key words: Dyslipidaemia; COVID-19; prevalence; mortality

Conflicts of interest: None of the authors have conflicts of interest to declare.

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Abstract

Objective: The prevalence and prognostic implications of pre-existing dyslipidaemia in patients infected by the SARS-CoV-2 remain unclear. To perform a systematic review and meta-analysis of prevalence and mortality risk in COVID-19 patients with pre-existing dyslipidaemia.

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 January 31, 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 effects models with odds ratio (OR) and related 95% CI. Statistical heterogeneity was measured using the Higgins I2 statistic.

Results: Eighteen 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).

Conclusions: 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.

Key words: Dyslipidaemia; COVID-19; prevalence; mortality

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 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. Aim of the present 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.

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 1) [7]. PubMed and Scopus databases were systematically searched for articles, published in English language, from inception through January 31, 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; (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 less

than 10 participants were excluded. Each included article was independently evaluated by two reviewers (MZ, LR); 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 (MZ, GR) using a standardized protocol. Disagreements were resolved. For this meta-analysis, the following data elements were extracted: sample size, number of survivors (S) and non-survivors (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 ± 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 effects 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, diabetes mellitus, arterial hypertension, chronic kidney disease, coronary artery disease, cerebrovascular events, and heart failure. 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 2, panel A). The relative funnel plot is presented in Figure 3, Panel A. 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 2, Panel B). Again, heterogeneity was high (I^2=88.7%).

Visual inspection of the relative funnel plot (Figure 3, Panel B) 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 to 0.025) and heart failure (HF) (p=0.001, coefficient 0.043, 95% CI 0.017 to 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 less than one 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-erm 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 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, the present 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 [33-37].

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 [38]. Moreover, when the viral infection has already occurred, increased levels of LDL-C may promote inflammasome activation and increased secretion of proinflammatory cytokines while lower HDL-C levels may trigger the dysregulation of the innate immune response [39]. 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 [40]. 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 CIVID-19 patients with history of dyslipidaemia might require a more aggressive therapeutical 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 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.

The present 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 [31-33].

Limitations

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

Conclusions:

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.

Declaration of competing interest: The authors declared they do not have anything to disclose regarding

conflict of interest with respect to this manuscript

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Figures

Figure 1. PRISMA flow diagram

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.

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

Supplementary files

Supplementary file 1. PRISMA Checklist

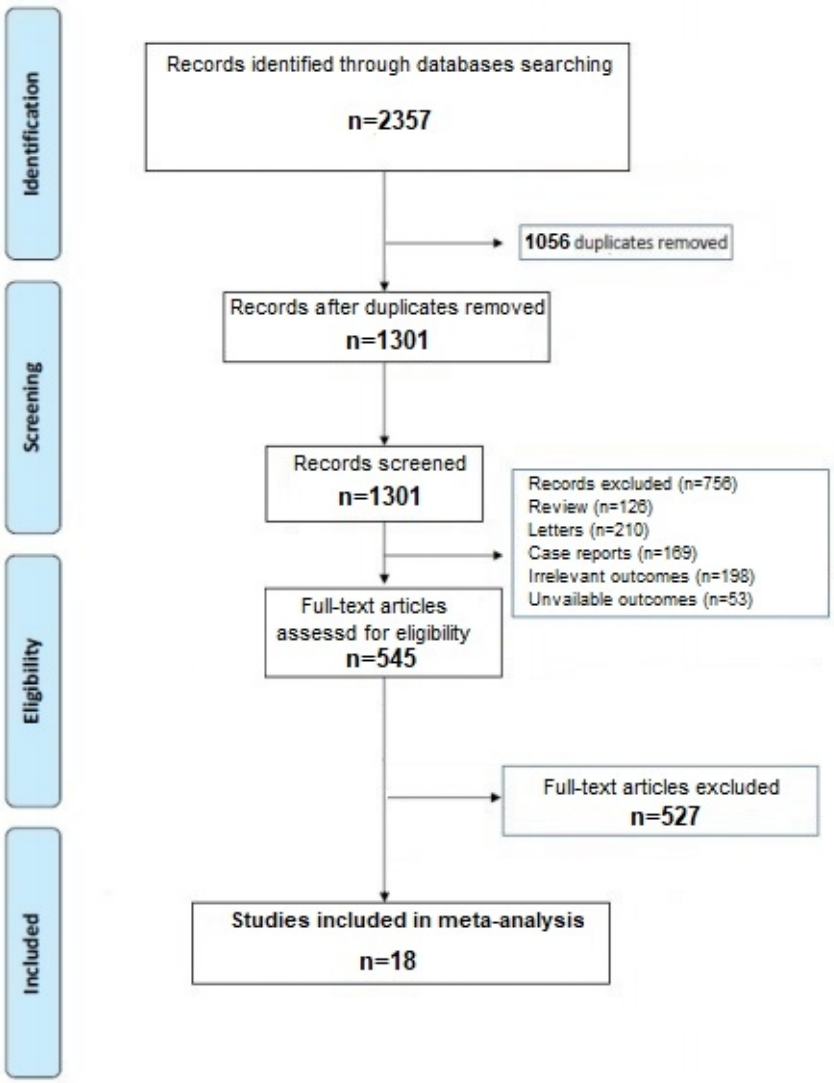
Author	Sample size	NS	S	Age (years) [IQR]; (SD)		Males N, (%)		DM N, (%)		HT N, (%)		NOS
				NS	*S*	*NS*	*S*	*NS*	*S*	*NS*	*S*	
Cipriani et al.	109	20	89	86 [77-87]	69** [57-79]	10 (50)	60 (71)	6 (30)	21 (24)	16 (80)	52 (58)	8
Ferrando et al.	663	203	460	68 [62-73]	65 [53-71]	47 (72.3)	310 (67.6)	61 (30.5)	90 (19.7)*	115 (54.6)	214 (46.5)*	8
Gayam et al.	408	132	276	71 [62-80]	63** [53-73]	76 (32.9)	155** (67.1)	72 (40.9)	104** (59)	105 (38.7)	166** (61.2)	8
Huang et al.	2623	232	2391	64 [49-73]	70 [63-78]	71 (30.6)	1229** (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** [41-61]	14 (36.8)	13.9 (44.7)	13 (34.2)	93 (23.9)	20 (52.1)	101* (32.5)	8
Yan et al.	1004	40	964	68 [58-79]	62* [50-70]	27 (67.5)	466* (48.3)	10 (25.0)	97* (10.1)	20 (50.0)	215** (22.3)	8
Mendes et al.	235	76	159	86.9 (6.4)	86.0 (6.5)	48 (63.1)	54** (33.9)	23 (30.3)	31* (19.5)	56 (73.7)	112 (70.4)	8
Chang et al.	106	30	76	75.5 (9.3)	65** (16.3)	19 (63.0)	35 (46.1)	17 (56.7)	25* (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** (48-72)	71 (63.9)	334 (56.6)	49 (43.8)	175* (29.7)	81 (73.4)	224** (37.9)	8
Rosenthal et al.	64781	7355	57426	74.2 (13.4)	53.7** (19.3)	4267 (58.0)	27701** (48.2)	3616 (49.1)	18091** (31.5)	5860 (79.7)	24376** (42.4)	8
Almazeedi et al.	1096	19	1077	55 (10.1)	38.7** (15.1)	16 (84.2)	872** (80.9)	6 (31.5)	149** (13.8)	8 (50.0)	169** (15.6)	7
Gomez-Antuner et al.	746	286	460	79 [74-86]	75** [66-82]	247 (86.7)	365* (79.4)	72 (25.4)	119 (26.1)	215 (75.7)	298** (65.0)	8

Rossi et al.	590	256	334	79.5 [74-84]	72.9 [64-80]	187 (73.0)	212* (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** (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

Table 1. Characteristics of studies included in the meta-analysis. NS: Non-survivors; S: Survivors; IQR: Interquartile range; SD: Standard deviation; DM; Diabetes mellitus; HT: Arterial Hypertension; NOS: Newcastle–Ottawa quality assessment scale. *p<0.05 between non-survivors and survivors; **p<0.001 between non-survivors and survivors.

Variable	Number of studies	Coefficient	SE	95% CI		P
				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	-0174	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

Table 2. Meta-regression analysis of the effects of presenting features on short-term mortality. BMI: Body mass index; DM: Diabetes mellitus; HT: Arterial hypertension; CKD: Chronic kidney disease; CAD: Coronary artery disease; CVE: Cerebrovascular events; HF: Heart failure; CI: Confidence interval; SE: Standard error.



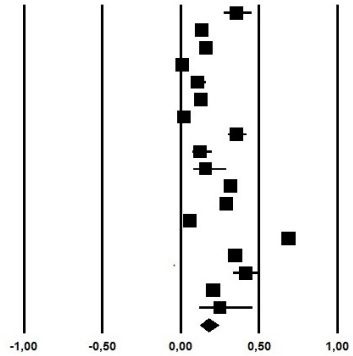
PRISMA flow diagram

129x164mm (96 x 96 DPI)

A

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Cipriani	0,358	0,274	0,452	-2,927	0,003	5,57
Ferrando	0,136	0,112	0,164	-16,325	0,000	5,77
Gayam	0,162	0,129	0,201	-12,237	0,000	5,73
Huang	0,008	0,005	0,012	-21,692	0,000	5,50
Kocaylgit	0,107	0,068	0,163	-8,530	0,000	5,42
Quisi	0,129	0,098	0,168	-11,960	0,000	5,67
Yan	0,020	0,013	0,031	-17,249	0,000	5,50
Mendes	0,357	0,299	0,421	-4,309	0,000	5,72
Chang	0,123	0,073	0,200	-6,645	0,000	5,26
Sun	0,160	0,082	0,289	-4,299	0,000	4,91
Cantenys-Molina	0,320	0,286	0,355	-9,332	0,000	5,81
Rosenthal	0,289	0,286	0,293	-103,708	0,000	5,86
Almazeedi	0,059	0,047	0,075	-21,612	0,000	5,74
Gomez-Antuner	0,688	0,653	0,720	9,990	0,000	5,82
Rossi	0,347	0,310	0,387	-7,289	0,000	5,81
Cho	0,413	0,335	0,495	-2,080	0,038	5,65
Lanza	0,207	0,166	0,254	-9,801	0,000	5,72
Saifi	0,250	0,117	0,456	-2,331	0,020	4,54
Random effect:	0,175	0,123	0,243	-7,320	0,000	

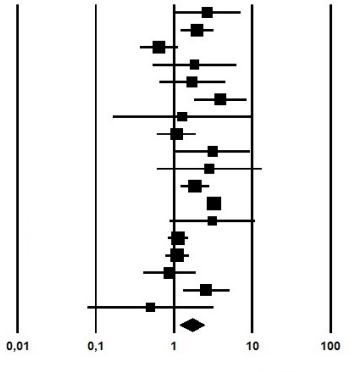
Tau-squared: 0.765
I-squared: 98.7%, p<0.0001



B

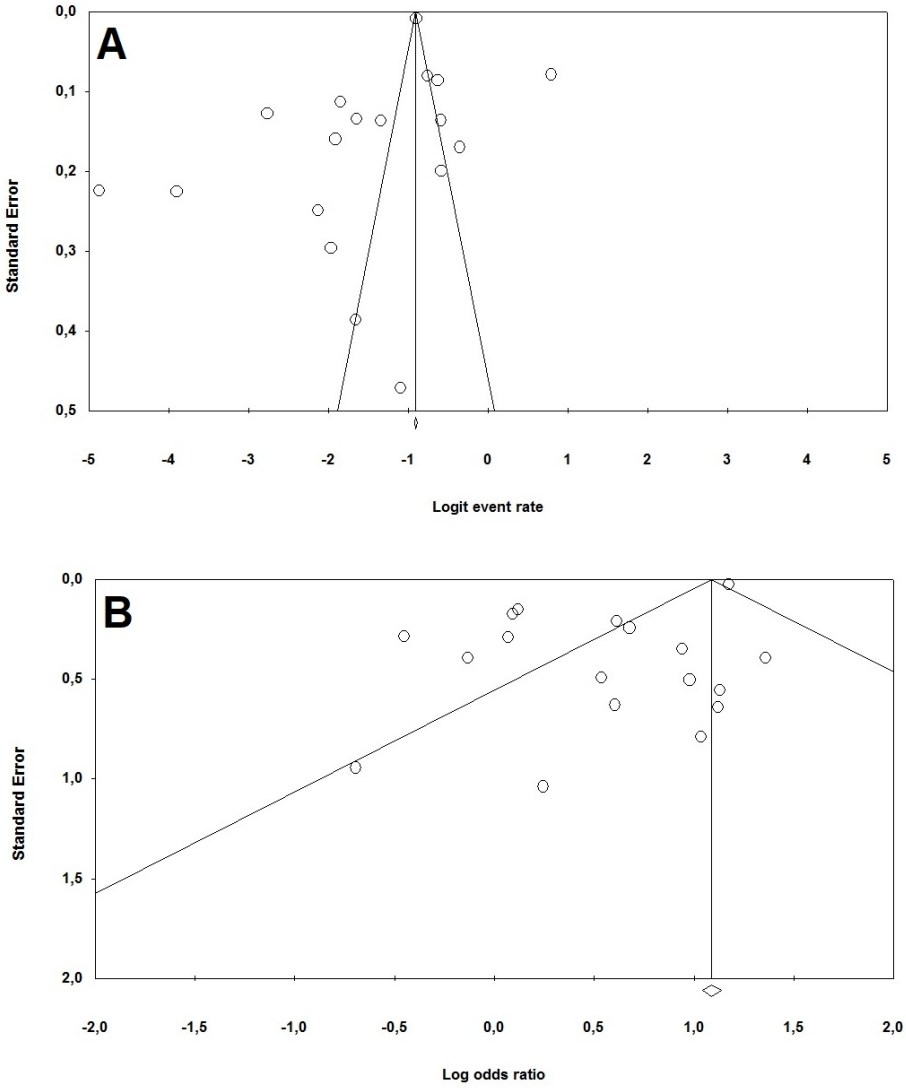
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Cipriani	2,663	0,991	7,152	1,943	0,052	4,97
Ferrando	1,970	1,220	3,179	2,775	0,006	7,11
Gayam	0,637	0,363	1,118	-1,571	0,116	6,77
Huang	1,830	0,532	6,292	0,959	0,337	4,07
Kocaylgit	1,710	0,652	4,489	1,090	0,276	5,06
Quisi	3,888	1,794	8,426	3,441	0,001	5,86
Yan	1,275	0,166	9,771	0,234	0,815	2,19
Mendes	1,073	0,608	1,894	0,243	0,808	6,74
Chang	3,091	1,038	9,207	2,026	0,043	4,58
Sun	2,818	0,600	13,241	1,312	0,189	3,17
Cantenys-Molina	1,844	1,220	2,788	2,905	0,004	7,35
Rosenthal	3,238	3,082	3,402	46,566	0,000	8,17
Almazeedi	3,070	0,871	10,816	1,745	0,081	3,99
Gomez-Antuner	1,125	0,837	1,513	0,782	0,434	7,74
Rossi	1,097	0,780	1,544	0,532	0,595	7,60
Cho	0,877	0,405	1,898	-0,334	0,739	5,87
Lanza	2,566	1,293	5,091	2,696	0,007	6,25
Saifi	0,500	0,078	3,186	-0,734	0,463	2,50
Random effect:	1,696	1,193	2,410	2,943	0,003	

Tau-squared: 0.393
I-squared: 88.7%, p<0.0001



(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.

312x350mm (96 x 96 DPI)



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

295x338mm (96 x 96 DPI)