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REVIEWS

Pre-existing atrial fibrillation is associated with increased mortality in COVID-19 Patients

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Abstract

Purpose The impacts of pre-existing atrial fibrillation (AF) on COVID-19-associated outcomes are unclear. We conducted a systematic review and meta-analysis to investigate the pooled prevalence of pre-existing AF and its short-term mortality risk in COVID-19 patients.

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 pre-existing AF among COVID-19 survivors and non-survivors. The pooled prevalence of pre-existing AF 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 I^2 statistic.

Results Twelve studies, enrolling 15.562 COVID-19 patients (mean age 71.6 years), met the inclusion criteria and were included in the final analysis. The pooled prevalence of pre-existing AF was 11.0% of cases (95% CI: 7.8–15.2%, $p < 0.0001$) with high heterogeneity ($I^2 = 95.2\%$). Pre-existing AF was associated with higher risk of short-term death (OR 2.22, 95% CI 1.47–3.36, $p < 0.0001$), with high heterogeneity ($I^2 = 79.1\%$).

Conclusion Pre-existing AF is present in about 11% of COVID-19 cases but results associated with an increased risk of short-term mortality.

Keywords Atrial fibrillation · COVID-19 · Prevalence · Mortality

1 Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and represents an important contributor to morbidity and mortality of general population [1]. Over the latest months, several studies have demonstrated that a history of cardiovascular disease, as well as de novo cardiovascular involvement, during COVID-19 infection is associated with a poor outcome [2–5]. To this regard, AF has been widely investigated in SARS-CoV-2 patients, due its high prevalence in general population, as an independent predictor of mortality, severe disease, or complication of the infection [6–8]. However, comprehensive analyses of these findings as well as data regarding the outcomes of COVID-19 patients with a history of AF are still scant. Aim of the present manuscript is to perform a systematic review and meta-analysis to evaluate the mortality risk associated with an history of AF in COVID-19 patients.

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2 Methods

2.1 Data sources and searches

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary File 1) [9]. 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. The informed consent was not required as the study did not enrol human subjects.

2.2 Study selection

Specifically, inclusion criteria were as follows: (i) studies enrolling subjects with a confirmed diagnosis of COVID-19 and (ii) studies stratifying the population as survivors (S) and non-survivors (NS), providing data on the pre-existing prevalence of AF. Conversely, studies presenting the prevalence of AF detected performing ECG at admission, the occurrence of AF as a complication of the infection, 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 (GR), and final consensus was achieved through discussion.

2.3 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 (hypertension (HT) and diabetes mellitus (DM)) stratified according to the outcome status (S and NS). Moreover, to perform a meta-regression, the following potential baseline confounders were also evaluated: prevalence of coronary artery disease (CAD), cerebrovascular events (CVE), heart failure (HF), and body mass index (BMI). The quality of included studies was graded using the Newcastle-Ottawa quality assessment scale (NOS) [10].

2.4 Outcomes

The prevalence of AF was chosen as the primary outcome, while the mortality risk due to a history of AF was selected as the secondary outcome.

2.5 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 AF (n/N), defined as the ratio between patients with history of AF (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 correspond with the following levels of heterogeneity: low (< 25%), moderate (25–75%), and high (> 75%) [11]. Considering that funnel plots have intrinsic limitations in detecting publication bias, we further carried out the Egger's regression test [12]. To further appraise the impact of potential baseline confounders, a meta-regression analysis was performed. The following variables were considered: age, BMI, gender, DM, HT, CAD, CVE, and HF. All meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, USA).

3 Results

3.1 Search results

A total of 2357 articles were obtained throughout our search strategy. After excluding duplicates and preliminary screening, 449 full-text articles were assessed for eligibility and 437 studies were excluded for not meeting the inclusion criteria, leaving 12 investigations fulfilling the inclusion criteria [13–24]. A flow diagram of the literature search and related screening process is shown in Fig. 1.

3.2 Study characteristics

Overall, 15,562 COVID-19 patients (mean age 71.6 years) were included in the analysis. The general characteristics of the analysed studies are summarized in Table 1. The mortality rate was 23.1% (95% CI 22.4–23.7). Overall, NS were older (77.9 vs 65.4 ears, $p < 0.001$), more frequently hypertensive, and diabetic compared to S. Quality assessment showed that all the studies were of moderate-high quality according to the NOS scale.

3.3 Pooled prevalence of AF

The prevalence of pre-existing AF among COVID-19 patients ranged between 0.5 and 21.8%. A random effect model revealed a pooled prevalence of pre-existing AF in 11.0% of cases (95% CI: 7.8–15.2%, $p < 0.0001$); heterogeneity was high ($I^2 = 95.2\%$) (Fig. 2). The relative funnel plot is presented in Fig. 4a. The Egger's test did not show publication bias ($t = 0.141$; $p = 0.890$).

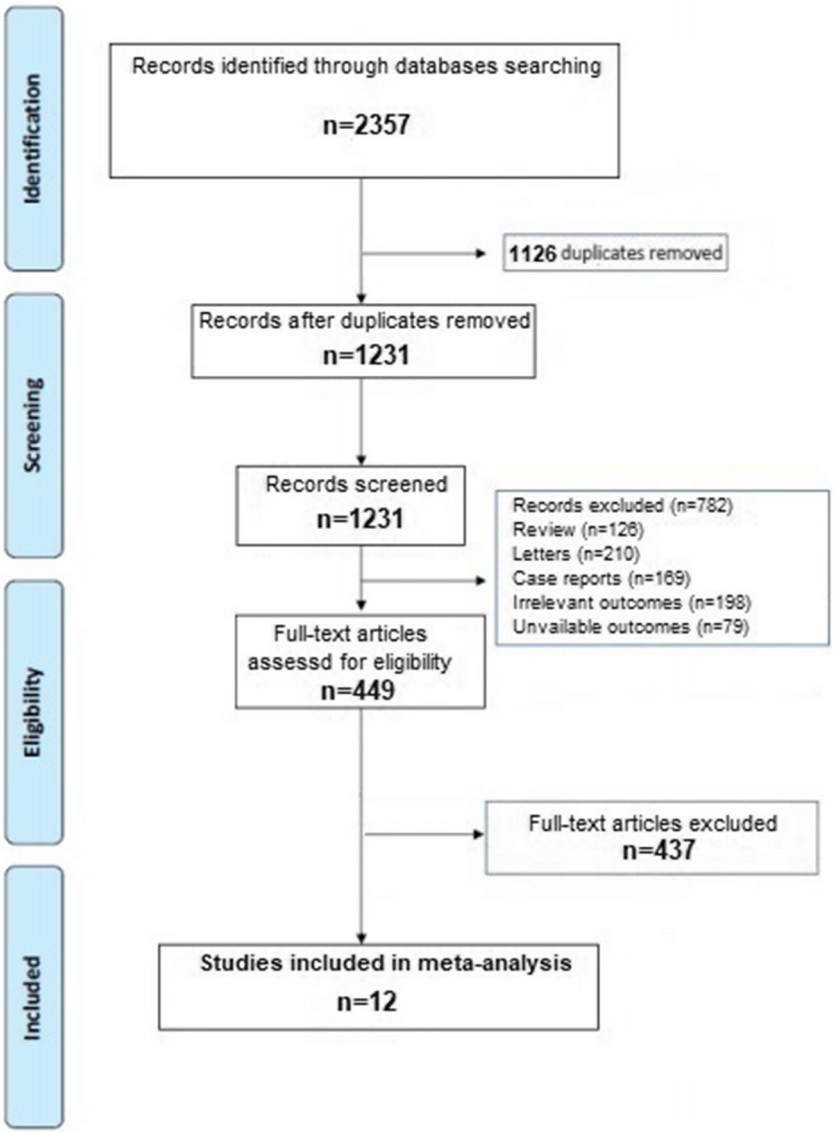

Fig. 1 PRISMA flow diagram

3.4 History of AF and mortality risk

On pooled analysis, pre-existing AF was significantly associated with a higher risk of death in the short-term period (OR 2.22, 95% CI 1.47–3.36, $p < 0.0001$) (Fig. 3). Again, heterogeneity was high ($I^2 = 79.1\%$). Visual inspection of the relative funnel plot (Fig. 4b) did not reveal evidence of publication bias as confirmed by the Egger's test ($t = 0.705$, $p = 0.496$).

3.5 Meta-regression

Meta-regression analysis revealed that the association between pre-existing AF and short-term mortality in COVID-19 patients was affected by age ($p = 0.011$), gender ($p = 0.032$), HT ($p = 0.001$), CAD ($p = 0.033$), and HF ($p = 0.0001$). Conversely, no association were identified considering BMI, CVE, and DM as moderator variables (Table 2). Multivariable meta-regression including significant covariates in a single analysis showed that age ($p = 0.368$), HT ($p = 0.210$), CAD ($p = 0.126$), and HF ($p = 0.421$) effect are probably dependent on each other.

4 Discussion

Our meta-analysis, which enrolled more than 15,000 COVID-19 patients, showed that pre-existing AF is present in about 11% cases and significantly increases the short-term mortality risk. This association was influenced by age, gender, HT, CAD, and HF. All these potential baseline confounders were inversely related with the effect of pre-existing AF on the short-term outcomes. Specifically, the association between pre-existing AF and short-term mortality in COVID-19 patients was higher in younger males' subjects without HT, CAD, and HF. Reason for such relationship can be found

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 (%)		Stroke N (%)		NOS
				NS	*S*	*NS*	*S*	*NS*	*S*	*NS*	*S*	*NS*	*S*	
Berrill et al. [13]	50	17	33	75 (10.9)	60.2 (21.2)*	6 (35.3)	16 (48.5)	8/16 (50.0)	9/31 (29.0)**	12 (70.6)	15/31 (48.4)*	NR		8
Mendes et al. [14]	235	76	159	86.9 (6.4)	86 (6.5)	48 (63.1)	54 (33.9)**	23 (30.3)	31 (19.5)	56 (73.7)	112 (70.4)	15 (20.3)	31 (19.6)	8
Quisi et al. [15]	349	38	311	69 [60–76]	55 [4–61]**	14 (36.8)	139 (44.7)	13 (34.2)	93 (23.9)	20 (52.6)	101 (32.5)*	2 (5.3)	5 (1.6)	7
Rodilla et al. [16]	12226	2630	9596	79.6 (10.5	64.1 (15.7)**	(61.9) §	(56.2)** §	23.2	16.6 **	70.6	45.5**	(14.2)§	(6.0)**	8
Cipriani et al. [17]	109	20	89	86 [77–87]	69 [57–79]	10 (50.0)	60 (71.0)	6 (30.0)	21 (24.0)	16 (80.0)	52 (58.0)	5 (25.0)	12 (14.0)	7
Knights et al. [18]	103	34	69	78.9	63.8**	20 (59.0)	38 (55.0)	14 (41.0)	10 (14.0)	18 (53.0)	28 (41.0)	11 (32)	5 (7)*	8
Shi et al. [19]	671	62	609	74 [66–81]	61 [49–70]**	35 (56.5)	287 (67.1)**	17 (27.4)	80 (13.1)*	37 (59.7)	162 (26.6)	8 (12.9)	14 (2.3)**	7
Rossi et al. [20]	590	334	256	79.5 [73–84]	73 [64–80]	187 (73.0)	212 (63.5)*	67 (26.2)	70 (21.0)	NR		8 (2.4)	13 (5.1)	7
Cho et al. [21]	143	36	107	75.8 (16.8)	68.5 (17.2)	20 (55.6)	68 (63.3)	9 (25.0)	41 (38.3)	16 (44.4)	63 (58.9)	NR		8
Gomez Antúnez et al. [22]	746	286	460	79 [74–86]	75 [66–82]	274 (86.7)	365 (79.4)	72 (25.4)	119 (26.1)	125 (75.74)	298 (65.0)	NR		8
Turgay Yidirim et al.[23]	139	26	113	71.8 (8.9)	44.0 (19.2)	19 (73.1)	66 (58.4)	9 (34.6)	12 (10.6)*	13 (50.0)	26 (23.0)*	NR		8
Denegri et al. [24]	201	42	159	79.9 (10.8)	65.6 (14.1)**	59.5 §	65.4 §	26.2 §	16.5 §	64.3 §	54.4 §	NR		7

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. §Only percentages reported

since older patients with such comorbidities may have a more aggressive treatments as both primary and secondary prevention, which partially reduces the risk of AF, especially in those with HF [25]. Our findings confirm the results of several investigations which demonstrated that the clinical outcomes in patients with SARS-CoV-2 infection are closely related to the burden of associated comorbidities [1–5, 26]. Moreover, our results fit well with a recent published meta-analysis evaluating the role of AF in COVID-19 patients in 108,745 patients. In fact, the authors underlined both a severe and worst outcome in COVID-19 patients with AF (OR 1.13, 95% CI 1.02–1.25) [27]. The presented results revealed a higher mortality risk, but our research was based on different study selection criteria, and our study did not focus only on AF patients, but analysed the published studies on COVID-19 patients stratifying their cohort among S and NS; therefore, the studies included in our meta-analysis are different from those considered by Yang et al. [27]. The inclusion of only subjects with pre-existing AF allowed us to limit the study bias since it has been reported that AF could be also a complication of infection. For this

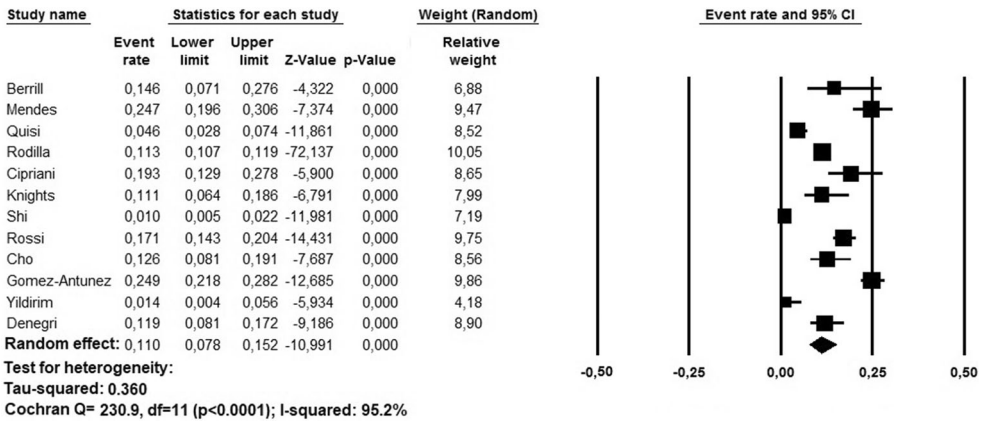

Fig. 2 Pooled prevalence of pre-existing atrial fibrillation in COVID-19 patients. CI, confidence interval

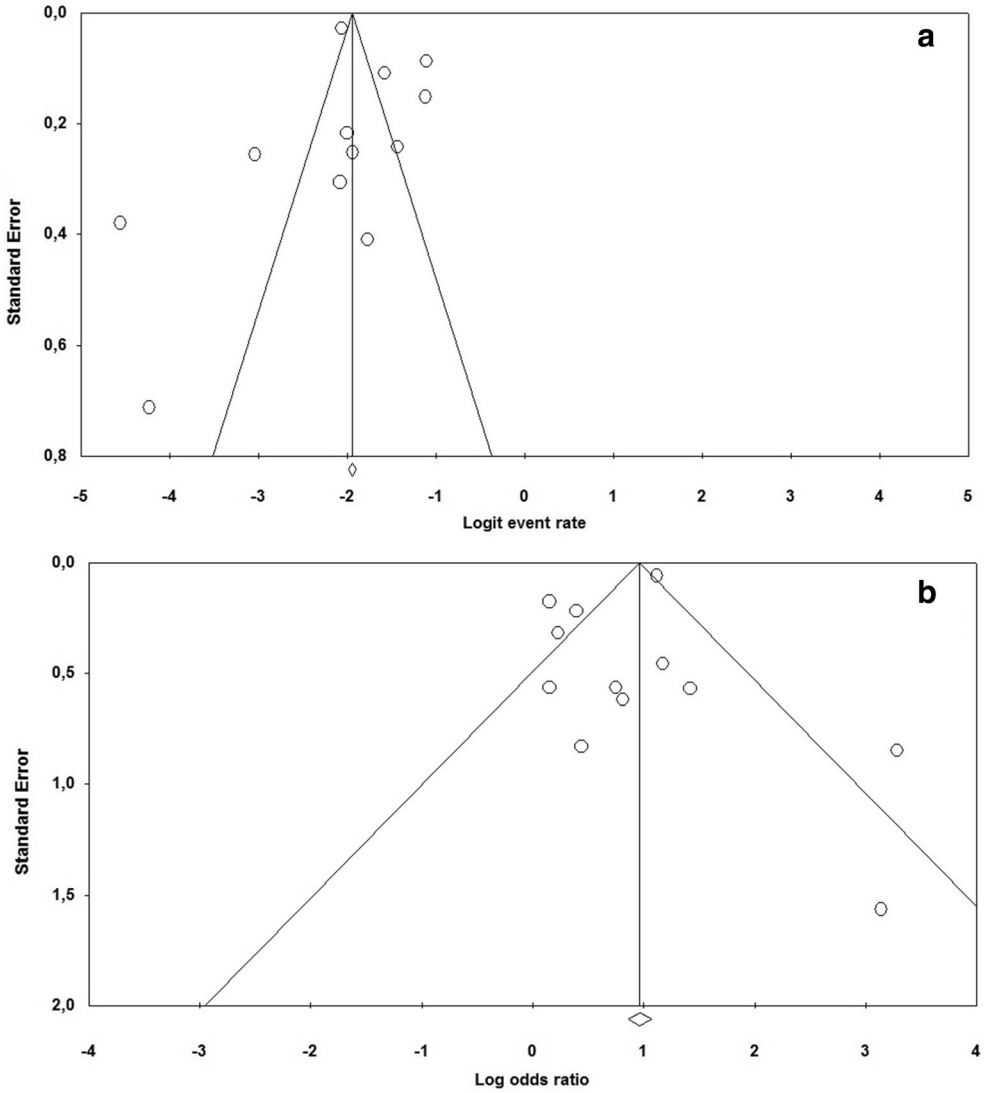

Fig. 4 Funnel plots for **a** the pooled prevalence of pre-existing atrial fibrillation in COVID-19 patients and **b** its associated mortality risk

reason, investigations defining the presence of AF only based on the first ECG at admission and not considering its anamnestic presence were excluded in order to avoid an overestimation of AF cases [24, 28, 29]. Several potential explanations for the association between COVID-19 infection and AF have been proposed; however, the exact underlying pathophysiology has

Study name	Statistics for each study					Weight (Random)
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Berrill	1,554	0,305	7,907	0,531	0,596	4,49
Mendes	1,259	0,675	2,347	0,725	0,469	11,21
Quisi	4,132	1,353	12,621	2,491	0,013	7,15
Rodilla	3,056	2,717	3,437	18,624	0,000	14,89
Cipriani	2,114	0,700	6,388	1,327	0,184	7,22
Knights	2,250	0,667	7,591	1,307	0,191	6,51
Shi	26,623	5,051	140,319	3,870	0,000	4,36
Rossi	1,483	0,965	2,278	1,796	0,072	12,95
Cho	1,166	0,385	3,533	0,272	0,786	7,20
Gomez-Antunez	1,166	0,825	1,647	0,872	0,383	13,62
Yildirim	23,163	1,078	497,782	2,008	0,045	1,61
Denegri	3,237	1,320	7,939	2,566	0,010	8,78
Random effect:	2,226	1,474	3,360	3,808	0,000	

Test for heterogeneity:
Cochran Q=52.6, df=11 (p<0.0001); I-squared= 79.1%
Tau-squared: 0.293

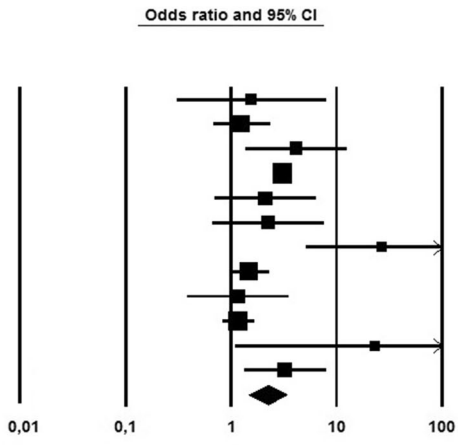

Fig. 3 Forest plot investigating the mortality risk due to pre-existing atrial fibrillation in COVID-19 patients using a random-effect model. CI, confidence interval

Table 2 Effects of baseline clinical characteristics on the pooled mortality risk due to pre-existing atrial fibrillation in COVID-19 patients assessed by meta-regression analysis

Variable	Number of studies	Coefficient	SE	95% CI		*p*
				Lower	Upper	
Age	12	-0.040	0.016	-0.072	-0.009	0.011
Gender (males)	12	-0.035	0.016	-0.068	-0.003	0.032
BMI	4	1.167	0.866	-0.530	2.864	0.177
HT	7	-0.055	0.017	-0.096	-0.021	0.001
CAD	7	-0.097	0.045	-0.187	-0.007	0.033
CVE	5	-0.055	0.036	-0.126	0.015	0.124
DM	12	-0.012	0.044	-0.100	0.075	0.781
HF	9	-0.045	0.011	-0.068	-0.022	0.0001

BMI body mass index, *HT* arterial hypertension; *CVE*: Cerebrovascular events; *CAD*; Coronary artery disease; *DM*: Diabetes Mellitus; *HF*: Heart Faiulre

not yet been clarified. In particular, it has suggested a direct interaction between SARS-CoV2 cardiac cells expressing ACE-2 receptors, as pericytes. To this regard, it has been proposed that SARS-CoV2 infection may interrupt the pericyte-endothelial interaction and cause micro-vascular leakage promoting the release of several biochemical factors in the attempt to restore this reciprocal paracrine crosstalk (i.e., VEGF, basic fibroblast growth factor, Ang1, Ang2). This process would contribute to local tissue inflammation and perturbation of atrial cellular electrophysiology. Other putative mechanisms include the reduction of angiotensin-converting enzyme 2 (ACE2) receptor availability; the atrial structural changes via CD147- and sialic acid-spike proteins; the hypoxemia; which may result in myocardial injury and remodelling; and the activation of sympathetic nervous system, which together with electrolytes and fluids disturbances would lead to atrial fibrillation susceptibility [30].

Unfortunately, among the revised investigations, only Quisi et al. [15] compared the CHA2DS2-VASc score between survivors and non-survivors, reporting higher values among the latter group ($p < 0.001$). Thus, we were not able to adequately explore the thromboembolic risk in the analysed cohort as well as the contributing role of anticoagulant treatments. Similarly, the considered studies did not systematically describe AF electrocardiographic features, making impossible firm conclusion on the role of AF in COVID-19 patients. In this regard, Cho et al., using continuous telemetry, reported the occurrence of atrial flutter in 3.5% of cases, while new onset AF during the hospitalization was observed in 5.6% of subjects. Moreover, no detail data regarding the type of AF and its duration were provided by the reviewed studies. Considering these elements, our results should be considered preliminary. Further larger and detailed analyses, considering the electrocardiographic and clinical characteristics as well, by the integration of data provided by continuous telemetry monitoring, are needed to better describe the association between AF and COVID-19 infection.

Our meta-regression analysed different potential confounding factors for AF such as gender, age, and pre-existing medical disorders. Age and gender resulted associated with the mortality risk in COVID-19 patients with pre-existing AF and COVID-19 infection. These findings are in accordance with previous analyses performed among general population demonstrating that AF, per se, is associated with aging and gender, as well as HT and CAD [31, 32]. On the other hand, no significant association was observed between BMI and mortality risk, as already suggested in a previous large trial demonstrating that both overweight and obesity in patients with non-valvular AF were associated with a lower risk for the composite outcome of stroke/all-cause death [33]. Despite that pre-existing CVE has been associated with poor outcomes in patients with COVID-19 infection [34], we did not find any correlation in our analysis, probably because not all the revised manuscripts reported data on the occurrence of such comorbidities and therefore our analysis underestimated this relationship. Intriguingly, DM resulted not to be associated with mortality risk. As known, DM represents an independent risk factor for AF. However, as reported by a recent meta-analysis, higher serum glycated haemoglobin levels were significantly associated with incident AF in prospective cohort studies, but not in retrospective case-control studies, as those included in our analysis [35].

Despite that the revised manuscript did not systematically performed multivariate regression analyses, or they did not consider AF as covariate, our findings are in accordance with other recent published investigations suggesting that AF represents an independent risk factor for mortality, irruptively from age and comorbidities such as DM and HT [6, 36]. These investigations have not been included in our analysis since they have not met the inclusion criteria of the present meta-analysis.

Based on our findings, COVID-19 patients with AF constitute a subset with an increased risk for short-term mortality, which may benefit from an early identification and more

aggressive surveillance/treatments since the first medical contact after the confirmation of SAR-CoV2- infection.

4.1 Limitations

We recognize some limitations to our study. Firstly, the observational and retrospective nature of the reviewed investigations (with their intrinsic and inherited biases) and the potential underestimation of pre-existing AF in the hospitalized patients may be responsible of the high heterogeneity in both the polled prevalence analysis and the mortality risk estimation. Furthermore, the absence of any adjustment for confounding relevant factors such as age, sex, baseline cardiovascular disease, anticoagulant treatments, and previous stroke in the reviewed studies have doubtless influenced the observed heterogeneity levels. Moreover, we could not investigate the effects of persistent AF versus paroxysmal AF on short-term mortality because the reviewed studies did not investigate this issue. Finally, we cannot evaluate the impact of different treatment strategies on the relationships between AF and short-term mortality.

5 Conclusions

The presence of pre-existing AF in COVID-19 patients is associated with an increased risk of short-term mortality, suggesting the need for closer monitoring and/or more aggressive treatments against the SAR-CoV-2 infection in these subjects.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10840-021-00992-2.

Authors' contributions Zuin M: conception; study design; writing the draft; data collection; data analysis. Rigatelli G: conception; study design; writing the draft; data collection; data analysis. Bilato C: revision; data collection; data analysis. Zanon F: data collection; revision. Zuliani G: data interpretation; critical revision. Roncon L: data interpretation; critical revision; supervision. All authors read and approved the final manuscript.

Data availability Available upon request.

Declarations

Informed consent Not applicable.

Conflict of interest Francesco Zanon reports speaker fees from Abbott, Biotronik, Boston Scientific, Medtronic, and Microport outside the submitted work. The other authors have no conflict of interest to report.

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