Incidence, Risk Factors, and Outcomes of Patients with COVID-19-Associated Pulmonary Aspergillosis (CAPA) in Intensive Care Units: A Systematic Review and Meta-Analysis Of 29 Cohort Studies

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Abstract

Background

Patients with Coronavirus disease 2019 (COVID-19) admitted to an intensive care unit (ICU) might develop COVID-19-related pulmonary Aspergillosis (CAPA). We aimed to identify studies systematically that describe the incidence and risks factors of CAPA, and to assess its outcome.

Methods

Two authors independently searched ScienceDirect, PubMed, CNKI, MEDLINE (OVID), and MedRXIV from December 31, 2019 to Feb 27, 2021. We included observational cohort studies that investigated patients with CAPA admitted to an ICU. We assessed the quality of all included studies using the Newcastle–Ottawa Scale). The meta-analysis was registered with PROSPERO (CRD42021242179).

Results

Twenty-nine cohort studies with 2095 patients with COVID-19 admitted to an ICU and 264 patients who developed to CAPA were included (Pooled incidence: 0.14, 95% confidence interval [CI] = 0.11–0.17). The overall mortality and case fatality rate of CAPA were 0.07 (0.05–0.09) and 0.51 (0.44–0.58), respectively. Patients with COVID-19 would develop CAPA at 7.28 days after mechanical ventilation (range, 5.48–9.08). Compared with patients without CAPA, those with CAPA had a significantly lower median body mass index (27.32 vs. 28.97 kg/m², $P = 0.034$), higher median creatinine level (127.94 vs. 88.23 μmol/L, $P = 0.014$), and were more likely to receive corticosteroids therapy (41.0% vs. 38.0%, risk ratio [RR] = 1.98, 95% CI=1.08–3.63) and renal replacement therapy (42.0% vs. 28.2%, RR = 1.61, 95% CI=1.04–2.50) during admission. Remarkably, patients with CAPA were associated significantly with a 1.66-fold higher mortality (RR = 1.66, 95% CI=1.31–2.12) without significant heterogeneity and publication bias.

Conclusions

Patients with COVID-19 admitted to an ICU might develop CAPA and have higher all-cause mortality. We recommend conducting prospective screening for CAPA among patients with severe COVID-19, especially for those who receive mechanical ventilation over 7 days.

Introduction

From December 2019, a pandemic of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly from Asia to the rest of the world [1]. About 5% of patients with COVID-19 require intensive care unit (ICU) management [2]. Clinicians are alert to the possibility of bacterial or fungal infection and prescribe antibiotics to nearly 90% of antibiotic patients with COVID-19 in the ICU setting [3]. Respiratory viruses (including SARSCoV-2) cause direct damage the airway epithelium [4], facilitating bacterial and fungi invasion. Furthermore, ciliary clearance is hampered by viral infection, resulting in immune dysfunction or dysregulation [5]. With severe pulmonary inflammation, longterm exposure to broad-spectrum antibiotics [6], and receipt of immunosuppressive drugs [7], patients with severe COVID-19 are at risk for secondary infections [8]. It was reported that 14% hospitalized patients with COVID-19 had bacterial co-infections in mixed ward or ICU settings [9]. Increasing numbers of studies have drawn attention to the high prevalence of COVID-19 associated pulmonary Aspergillosis (CAPA) in patients with severe COVID-19 [2, 10–12] admitted to the ICU. A diagnosis of CAPA was made based on specific case definitions or diagnostic algorithms, including the AsplCU algorithm, Modified AsplCU algorithm, influenza-associated pulmonary aspergillosis (IAPA) criteria, the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group, the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG), the European Confederation for Medical Mycology, and the International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria. However, the exact incidence of CAPA remains unknown and opinions are polarized [13–16]. Currently, reports on the incidence, risk factors, and outcomes of CAPA remain inconclusive. To address this gap in the literature, we conducted this systematic review and meta-analysis of 29 cohort studies, with the aim of identifying studies that describe the incidence and risks factors of CAPA, and then assessing the outcome of CAPA.

Methods

This systematic review was based on a prospectively registered protocol (PROSPERO CRD42021242179) and was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The review process is illustrated in a flow diagram (Figure 1).

Search Strategy

A search string was developed to identify original research studies reporting clinical characteristics and outcomes of patients with CAPA. The search was applied to the following databases: ScienceDirect, PubMed, CNKI, MEDLINE (OVID), and MedRXIV. Searches were performed for each database from December 31, 2019 to Feb 27, 2021. The following key words were used in all database searches: “coronavirus”, “COVID”, “COVID-19”, “severe acute respiratory syndrome”, “coronavirus 2”, “SARS-CoV-2”, “Aspergillus”, “pulmonary Aspergillus”, “invasive Aspergillus”, “invasive pulmonary Aspergillus”, “COVID-19-Associated pulmonary Aspergillosis” and “intensive care unit”.

Study Selection and Eligibility Criteria

All references were collected and screened independently by two reviewers (Chen WS and Kai Zhang) against a set of predefined eligibility criteria. Potentially eligible studies were selected for full-text analysis. Disagreements were resolved by consensus or by appeal to a third senior reviewer (Liu Y). All observational cohort studies reporting the incidence and outcome of CAPA among patients with COVID-19 admitted to an ICU were included in this meta-analysis. The exclusion criteria included case control studies, case reports, nonhuman research, and meeting abstracts without a full article.

Quality Assessment

The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) by the two researchers who were involved in the literature search (Chen WS and Zhang K), who assessed the quality of all included studies and discussed discrepancies until a consensus was reached with the corresponding author (Zhuang GH).

Data Extraction and Outcome Measures

Data were extracted for the following variables: study period, sample size, definition of CAPA, age, sex, underlying disease, laboratory examination, exposure information of CAPA, and outcome. Mortality was defined as the number of deaths diagnosed with CAPA divided by the number of COVID-19 cases in the cohort. The case fatality rate (CFR) was defined as the number of CAPA deaths divided by the total number of CAPA cases in the cohort. The primary outcome was all-cause mortality and all-cause CFR during admission. The secondary outcome was the length of ICU stay for the patients with COVID-19.

Statistical Analysis

Random-effects meta-analysis [18] was used to reported the incidence, all-cause mortality, all-cause CFR, and risk ratios (RRs) with 95% confidence intervals (CIs). For pooling of the means of numerical variables, we computed missing means and standard deviations (SDs) from medians; ranges (minimum to maximum); and inter-quartile ranges (IQRs); using the methods proposed by Hozo et al. [19]. Pooled proportions were computed using the inverse variance method and the variance-stabilizing Freeman-Tukey double arcsine transformation [20]. Subgroup analysis was conducted based on the literature design (prospective or retrospective study), the type of research centre (Single or Multi-centre), and the clinical characteristics of the patients (e.g., acute respiratory distress syndrome (ARDS), acute respiratory failure (ARF)). The Mantel–Haenszel estimator was used to calculate the between-study heterogeneity statistic Q , which was used in the DerSimonian–Laird estimator. The I^2 statistic was used to present between-study heterogeneity, where $I^2 \geq 50\%$ was considered substantial. We assessed publication bias using Egger's test and by inspecting funnel plots. Statistical analyses were performed using the R software version 3.6.3 (R Foundation for Statistical Computing, 2016), with the package “meta” and Stata Special Edition 15.1 (Stata Corp, College Station, TX, USA). P -values less than 0.05 were considered statistically significant.

Results

Our search algorithm in the MEDLINE, OVID, PubMed and MedRxiv databases retrieved 1441 records. We screened based on the title and abstract and excluded 1377 studies. Sixty-four articles were assessed for eligibility. Finally, we identified 29 observational cohort studies that qualified according to our predefined inclusion and exclusion criteria (Figure 1), which included a total of 2095 patients with COVID-19 admitted to an ICU.

Characteristics of included studies

Of the 29 studies, 8 (27.59%) were from France [2, 13, 21–26], 4 (13.79%) were from the United Kingdom (UK) [27–32], 4 (13.79%) were from the Netherlands [33, 34], 2 (6.90%) were from Germany [35, 36], 2 (6.90%) were from Spain [15, 37], 2 (6.90%) were from Switzerland [14, 38], 1 (3.45%) was from the USA [39], 1 (3.45%) was from Belgium [40], 1 (3.45%) was from China [6], 1 (3.45%) was from Pakistan [41], 1 (3.45%) was from Denmark [42], 1 (3.45%) was from Italy [43] and 1 (3.45%) from Mexico [44]. Twelve studies dealt with patients who received mechanical ventilation, eight studies were of patients with ARDS, one study was on extracorporeal membrane oxygenation (ECMO), 1 study looked at acute respiratory failure (ARF), and seven studies included other patients with severe COVID-19 (See additional file 1, supplementary 1).

Quality control of included studies

The risk of bias included in the cohort studies was assessed using the Newcastle–Ottawa–Scale (NOS) as presented in Table 1. The overall score was 141 out of 232 (60.78%), which is considered to be indicative of moderate quality. All the eligible studies included patients with severe COVID-19 admitted to ICU. Among the studies, 34.48% (10/29) did not describe the determination of exposure. In addition, 72.41% (21/29) studies did not control the comparability of the cohorts on the basis of the design or analysis. Although all studies (29/29) followed up the patients for long enough for defined outcomes to occur, only 51.72% (15/29) demonstrated clearly the adequacy of follow up of the cohorts. All studies assessed the outcomes of interest based on medical record linkage (See additional file 1, supplementary 2).

Incidence of CAPA

In the studies, 2095 patients with severe COVID-19 admitted to an ICU were investigated and 264 cases of CAPA were reported. The incidence of CAPA was calculated as 0.14 (95% confidence interval [CI] = 0.11–0.17, $I^2 = 81.2\%$). In the sub-group analysis by study design, the incidence of CAPA was calculated at 0.14 (95% CI = 0.09–0.19, $I^2 = 87.4\%$) in the prospective studies and 0.14 (95% CI = 0.10–0.18, $I^2 = 74.1\%$) in the retrospective studies (Table 1). When stratified analysis was undertaken by research centre (multi-centre or single centre), the CAPA incidence was 0.12 (95% CI = 0.10–0.15, $I^2 = 77.3\%$) for the single centre studies and 0.20 (95% CI = 0.12–0.28, $I^2 = 81.2\%$) for the multi-centre studies. We found a high heterogeneity for calculation of the incidence of CAPA and significant publication bias according to Egger's regression test (See additional file 1, supplementary 3 Figure A). Remarkably, we found that patients with COVID-19 admitted to an ICU would develop CAPA after approximately 7.28 days of mechanical ventilation (nine studies, 95% CI = 5.48–9.08, $I^2 = 46\%$) (Figure 2).

Colonisation by *Aspergillus*

In five cohort studies including 365 patients with COVID-19 admitted to an ICU, 21 patients were assessed for *Aspergillus* colonisation. The calculated colonization rate of was 5.75% (21/365) (See additional file 1, supplementary 1), suggesting that clinicians should comprehensively analyse *Aspergillus* colonisation combined with other clinical evidence (such as imaging and inflammatory factors, etc.) to judge whether the patient might develop CAPA and require further anti-fungal treatment.

All-cause mortality of CAPA

Twenty-three studies were included in the final analysis, with 119 deceased patients and 2786 surviving patients. The overall mortality of CAPA was 0.07 (95% CI = 0.05–0.09, $I^2 = 64.2\%$) among patients with severe COVID-19. In the subgroup analysis for study design, the calculated all-cause mortality of CAPA was 0.07 (95% CI = 0.04–0.10, $I^2 = 67.1\%$) for the prospective studies, 0.08 (95% CI = 0.05–0.11, $I^2 = 62.9\%$) for the retrospective studies, 0.06 (95% CI = 0.09–0.09, $I^2 = 0\%$) for the single centre studies, and 0.11 (95% CI = 0.06–0.16, $I^2 = 0\%$) for the multi-centre studies. There was significant publication bias on Egger's regression test (Table 1).

CFR of CAPA

Twenty-three studies were eligible for further analysis of all-cause CFR with 119 deceased patients and 145 surviving patients. We found that the pooled CFR was 0.51 (95% CI, 0.44–0.58, $I^2 = 86.5\%$). In the subgroup analysis by study design, the calculated CFRs were 0.49 (95% CI, 0.39–0.59, $I^2 = 88.4\%$) for the prospective studies, 0.53 (95% CI = 0.43–0.63, $I^2 = 85.9\%$) for the retrospective studies, 0.50 (95% CI = 0.42–0.58, $I^2 = 86.5\%$) for the single centre studies, and 0.58 (95% CI = 0.42–0.73, $I^2 = 89.5\%$) for the multi-centre studies (Table 1).

Comparing patients with CAPA with those without CAPA (control)

Risk factors for CAPA

Eleven studies were pooled to investigate and compared patients with and without CAPA (127 vs. 788 patients) (Table 2). No significant differences were observed regarding general population characteristics (age, sex, hypertension, diabetes, obesity, cardiovascular disease, history of cancer, chronic pulmonary disease, chronic kidney disease, an immunosuppression), blood examination (white blood cell [WBC] count, neutrophil count, lymphocyte count, creatinine, C-reactive protein [CRP], and lactate dehydrogenase (LDH)), and respiratory sample characteristics at baseline (Table 2). Compared to patients without CAPA (control), patients with CAPA had a significantly lower median BMI (four studies, 27.32 vs. 28.97 kg/m², $P = 0.034$) and higher median creatinine (four studies, 127.94 vs. 88.23, $P = 0.14$). No differences in the use of Lopinavir/ritonavir, Hydroxychloroquine (HCQ), Azithromycin, Tocilizumab, ventilated prone, and ECMO were observed in the patients with CAPA compared with those without (Table 2). However, compared with the controls, patients with CAPA were more likely to have received corticosteroids during admission (eight studies, 41.0% [41/100] vs. 38.0% [273/719], risk ratio [RR] = 1.98, 95% CI = 1.08–3.63, $I^2 = 74.10\%$) and renal replacement therapy (two studies, 42.0% [29/69] vs. 28.2% [90/319], RR = 1.61, 95% CI = 1.04–2.50, $I^2 = 32.5\%$) (Table 2).

Outcome with CAPA or without CAPA

Eleven studies were included. The analysis showed that patients with CAPA were associated significantly with a 1.66-fold higher risk for mortality (risk ratio [RR] = 1.66, 95% CI = 1.31–2.12, $I^2 = 22.5\%$) (Figure 3) without significant heterogeneity and publication bias (See supplementary 3). In the subgroup analysis by study design, patients with CAPA were associated significantly with a 1.53-fold elevated risk of mortality (six studies, RR = 1.53, 95% CI = 1.02–2.21, $I^2 = 47.9\%$) for the retrospective cohort studies, a 1.93-fold elevated risk of mortality (five studies, RR = 1.93, 95% CI = 1.37–2.71, $I^2 = 0\%$) for the prospective cohort studies (Figure 3 A), a 1.52-fold elevated risk of mortality (nine studies, RR = 1.52, 95% CI = 1.12–2.07, $I^2 = 24.7\%$) the for single centre studies, and a 2.03-fold elevated risk of mortality (two studies, RR = 2.03, 95% CI = 1.46–2.81, $I^2 = 0\%$) for the multi-centre studies (Figure 3 B). No statistically significant difference was found in the length of ICU stay for CAPA and non-CAPA patients (MD = 5.58, 95% CI = -1.93 to 13.08, $P = 0.145$) (Table 2).

Discussion

We conducted this systematic review of 29 cohort studies and observed that 14% of patients with COVID-19 admitted to the ICU developed CAPA. Meanwhile, the median time to develop CAPA among patients with COVID-19 who received mechanical ventilation was 7.28 days. Studies reported that the incidence of CAPA varied from 1.9–27.7% [14, 43, 45]. This wide divergence might result an underestimate of the risk of CAPA. Invasive pulmonary Aspergillosis is a secondary infection of severe respiratory viral infection [46, 47] and these infections have been related with significant morbidity and mortality, even when appropriately diagnosed and treated [48]. CAPA not only occurred in immunosuppressed patients (e.g., those with acute myeloid leukaemia) [49], but also in immunocompetent patients with COVID-19 [48, 50]. COVID-19 was independently associated with CAPA [36]. However, we observed significant heterogeneity in the pooled analysis of CAPA incidence. Many hospitals do not commonly perform bronchoscopy for CAPA diagnosis or use PCR tests for *Aspergillus* species[51]. Non-standardized definitions of CAPA (See additional file 1, supplementary 4), differences in detection methods [52], and variations among research designs might have contributed to heterogeneity across the studies, which requires further investigation. Nevertheless, we still recommend that clinicians should be alert to the occurrence of CAPA in patients with COVID-19, especially in those receiving mechanical ventilation more than 7 days.

The patients with COVID-19 who had higher APACHE II scores [36] and complicated underlying diseases (such as hypertension, diabetes, and tumours) [53], were independently associated with CAPA. We found that patients with CAPA had a lower BMI and higher concentration of creatinine compared with those without. One study indicated that elevated serum creatinine level was an independent risk factor for neutropenia-related invasive Aspergillosis [54]. The roles of BMI and creatinine in CAPA deserve further investigation. In this study, no differences in use of Lopinavir/ritonavir, HCQ, Tocilizumab, ventilated prone, and ECMO were observed in the patients with CAPA (As shown in Table 2). However, patients with CAPA were more likely to have received corticosteroid therapy and renal replacement therapy during admission compared with the non-CAPA controls. Previous studies reported that the use of corticosteroids increased the

risk of invasive pulmonary Aspergillosis significantly after severe viral infection (Influenza) [55]. Patients requiring dialysis and kidney transplantation were also at risk of invasive Aspergillosis [56]. Existing evidence supported the view that the use of corticosteroids and renal replacement therapy might play an important role in the progression of patients with COVID-19 with CAPA.

We pooled 11 cohort studies and observed that the patients with CAPA were associated significantly with a 1.66-fold higher risk of mortality (1.66, 95% CI = 1.31–2.12, $I^2 = 22.5\%$) (Fig. 3) without significant heterogeneity and publication bias (See additional file 1, Supplementary 3 Figure D). The findings supported the view that patients with CAPA had uniformly worse outcomes compared to those without, regardless of the definitions used. Meanwhile, we investigated the outcome of CAPA and found that the overall mortality of CAPA in COVID-19 patients in the ICU was 0.07 (Pooled mortality = 0.07, 95% CI = 0.05–0.10). The occurrence of CAPA would exacerbate the deterioration of respiratory function, thus increasing the risk of death. We pooled the studies and found that the all-cause CFR of patients with CAPA was 51%. Among all included studies, a very high proportion of patients with COVID-19 received mechanical ventilation. The proportion of patients receiving baseline mechanical ventilation in the 13 studies was more than 89% (11 studies, 100% mechanical ventilation). A systematic review has revealed that the CFR of patients with COVID-19 receiving mechanical ventilation was 45% (95% CI, 39–52%) [57]. Meijer and others conducted a small-sample cohort study (66 ICU patients with COVID-19) and found that the incidence of CAPA was 19.7% ($n = 13/66$), and the fatality rate of a single study was 46.2% (6/13); the author's team listed some of the articles that have been published and analysed for the CAPA fatality rate. The pooled CFR for CAPA was 47% (62/132) [32].

The NOS was used to evaluate the quality of the included articles. We found that the selected studies were of medium quality (60.78%). The most often overlooked factors were the representativeness of the exposed cohort, determination of exposure, comparability of the cohorts on the design or analysis, and the adequacy of the follow up of the cohorts (these four factors were scored as 0%, 34.48%, 27.59%, and 51.72%, respectively), which should be improved in future cohort studies. Meanwhile, we pooled the studies to investigate the incidence of CAPA incidence and CFR, and observed significant research heterogeneity. On the one hand, because of the lack of comparison of individual rates, heterogeneity occurred easily [57]. On the other hand, there was lack of a unified definition of CAPA (See supplementary 4) and a standard diagnostic algorithm in the published studies. Although we strictly controlled quality based on the study entry and exclusion criteria, heterogeneity between studies was still unavoidable. This meta-analysis did not explore the risk factors for mortality in patients with CAPA because of insufficient literature support. Further well designed research and demonstration would be warranted in the future.

Conclusion

In this study, the pooled incidence of CAPA was estimated as 14% among patients with COVID-19 admitted to the ICU, with high rate of all cause-mortality and CFR. We recommend that clinicians establish standardized screening methods for CAPA and to identify high risk patients early, especially for patients who have been mechanically ventilated for more than 7 days. Host factors (BMI and creatinine level) and the treatment of COVID-19 (the use of corticosteroids and renal replacement therapy) would significantly affect the development of CAPA.

Abbreviations

COVID-19: Coronavirus disease 2019

CAPA: COVID-19-Associated pulmonary Aspergillosis

ICU: Intensive care unit

CFR: case fatality rate

RR: Risk ratio

MD: Mean difference

CI: Confidence intervals

Declarations

Availability of data and materials

The datasets synthesized during the current study are available from the corresponding author on reasonable request.

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Contributions

CWS and ZK searched the literature, collected the data, assessed the quality of references, and performed statistical analyses. CWS and CY drafted the manuscript. ZM, HBJ and GXD directed, reviewed, and revised the manuscript. LY and ZGH conducted the study design, supervised the collection of data and statistical analyses. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All other authors have no conflicts of interest to declare.

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Tables

Table 1 The incidence, mortality and CFR of CAPA among all 29 included studies

Variable	Incidence of CAPA					Mortality of CAPA					CFR of CAPA	
	References	CAPA patients/Total	Effect	95% CI	I^2 (%)	References	Deceased/Total	Effect	95% CI	I^2 (%)	References	Deceased/CAPA patients
Overall	29	264/2095	0.14	0.11-0.17	81.2	23	119/2095	0.07	0.05-0.10	64.2	23	119/264
Study design												
Prospective	11	124/1041	0.14	0.09-0.19	87.4	10	58/1041	0.07	0.04-0.10	67.1	10	58/124
Retrospective	18	140/1054	0.14	0.10-0.18	74.1	13	61/1054	0.08	0.05-0.11	62.9	13	61/140
Centers												
Single-center	26	194/1744	0.12	0.10-0.15	77.3	20	78/1744	0.06	0.03-0.09	0	20	78/194
Multi-center	3	70/351	0.20	0.12-0.28	81.2	3	41/351	0.11	0.06-0.16	0	3	41/70
Characteristics												
MV	12	98/932	0.11	0.07-0.15	77.5	9	46/932	0.06	0.03-0.09	64.1	9	46/98
ARDS	5	40/239	0.16	0.11-0.20	0	5	20/239	0.08	0.04-0.11	0	5	20/40
ARDS, MV	3	44/243	0.17	0.04-0.30	86.8	2	15/243	0.08	0.01-0.16	66.9	2	15/44
ARF, MV	1	11/32	0.34	0.18-0.51	0	1	4/32	0.13	0.01-0.24	0	1	4/11
ECMO	1	2/8	0.25	-0.05-0.55	0	1	2/8	0.25	-0.05-0.55	0	1	2/2
Unknown	7	69/641	0.14	0.07-0.21	86.5	5	32/641	0.08	0.02-0.13	82.1	5	32/69

Abbreviation: CFR, case fatality rate; MV, mechanical ventilation; ARDS, acute respiratory distress syndrome;

Table2 Pooled analysis of risk factors compared CAPA with Non-CAPA patients among 11 cohort studies

Variable	References (N) ^a	CAPA	Non-CAPA (Control)	Random effects model			I ² (%)	P value for heterogeneity
		Event/Total or mean±SD	Event/Total or mean±SD	Effects (RR or MD)	95% CI	P- value		
Age (years), Mean±SD	8	63.84±1.18	60.40±1.58	1.65	[-0.99- 4.30]	0.220	0.00	0.686
Men, N	9	85/111	436/562	0.77	[0.46- 1.29]	0.326	0.00	0.594
BMI (Kg/m2), Mean±SD	4	27.32±0.83	28.97±0.47	-1.19	[-2.28 - -0.09]	0.034	3.60	0.375
Underlying disease								
Hypertension , n/N	6	43/78	187/395	1.41	[0.63- 3.13]	0.399	44.40	0.109
Diabetes, n/N	8	28/105	162/537	0.96	[0.58- 1.57]	0.863	0.00	0.965
Obesity, n/N	5	32/78	256/453	0.72	[0.42- 1.25]	0.247	0.00	0.473
CVD, n/N	3	5/39	17/138	1.28	[0.41- 4.04]	0.672	1.00	0.364
Chronic pulmonary disease (e.g. , COPD, Asthma), n/N	6	15/84	35/392	2.49	[0.92- 6.62]	0.072	39.9	0.140
CKD, n/N	3	8/48	13/124	1.78	[0.66- 4.84]	0.258	1.10	0.364
Immunosuppression, n/N	3	5/36	11/160	2.93	[0.68- 12.53]	0.148	26.50	0.256
Blood examination								
WBC(10 ⁹ /L), Mean±SD	3	9.74±1.07	8.44±0.64	1.63	[-0.60- 3.85]	0.152	0.00	0.679
Neutrophil count (10 ⁹ /L), Mean±SD	2	8.02±1.18	6.69±0.60	1.37	[-1.32- 4.07]	0.318	12.30	0.286
Lymphocyte count (10 ⁹ /L), Mean±SD	2	0.75±0.06	0.79±0.04	-0.04	[-0.19- 0.12]	0.651	12.60	0.285
Creatinine (μmol/L), Mean±SD	4	127.94±13.13	88.23±7.09	33.32	[6.81- 59.83]	0.014	0.00	0.739
CRP(mg/L), Mean±SD	4	138.84±21.11	173.95±22.01	-18.20	[-51.86- 15.47]	0.289	0.00	0.539
LDH (IU/L), Mean±SD	2	561.01±171.56	579.03±179.60	-5.81	[-67.70- 56.08]	0.854	0.00	0.861
Respiratory sample characteristics in baseline								
PaO2/FiO2	6	118.44±21.06	125.54±16.06	-1.72	[-14.90- 11.46]	0.798	0.00	0.629
SAPS II	3	52.59±11.77	40.87±1.15	11.43	[-10.86- 33.73]	0.315	75.10	0.018
SOFA	4	7.38±2.84	6.06±1.43	1.36	[-0.12- 2.88]	0.079	60.80	0.054
COVID-19 therapy								
Lopinavir/ritonavir	2	18/51	37/160	1.51	[0.68- 3.37]	0.311	59.50	0.116
HCQ	2	35/51	96/160	0.99	[0.89- 1.10]	0.851	0.00	0.710
Azithromycin	2	18/51	48/112	1.24	0.41- 3.75	0.707	83.9	0.013
Corticosteroids	8	41/100	273/719	1.98	[1.08- 3.63]	0.027	74.10	<0.001
Tocilizumab	4	33/72	157/483	1.43	[0.80- 2.57]	0.233	70.50	0.017

Ventilated Prone	2	27/41	68/103	1.16	[0.56-2.39]	0.692	77.4	0.036
ECMO	2	4/28	79/225	0.77	[0.35-1.71]	0.517	0.00	0.567
RRT	4	29/69	90/319	1.61	[1.04-2.50]	0.033	32.50	0.217
Outcome								
Mortality, n/N	11	65/127	322/788	1.66	[1.31-2.12]	<0.001	22.50	0.229
Length of ICU stay (days), Mean±SD	8	24.61±2.79	20.80±1.75	5.58	[-1.93-13.08]	0.145	68.50	0.002

^a, the field including only one study will not be pooled and shown; Abbreviation: CVD, Cardiovascular diseases; CKD, chronic kidney disease; RRT, Renal replacement therapy

Figures

Figure 1

Flow Diagram of this study

Figure 2

Time window of the patients developed CAPA

Figure 3

Comparison of the outcome of COVID-19 patients admitted to ICU with and Without CAPA A: Sub-group analysis by study design (Single Center or Multi-Center); B: Sub-group analysis by study design (Prospective or Retrospective)

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