

Risk Factors of Severe Disease and Efficacy of Treatment in Patients Infected with COVID-19: A Systematic Review, Meta-Analysis and Meta-Regression Analysis

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Summary:

Predictors of intensive care unit admission, mortality and acute respiratory distress syndrome in COVID-19 patients were identified. Lopinavir-ritonavir treatment did not show significant benefit, whereas corticosteroid use was associated with poorer outcome.

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic spread globally in the beginning of 2020. At present, predictors of severe disease and the efficacy of different treatments are not well-understood. We conducted a systematic review and meta-analysis of all published studies up to March 15, 2020 which reported COVID-19 clinical features and/or treatment outcomes. 45 studies reporting 4203 patients were included. Pooled rates of intensive care unit (ICU) admission, mortality and acute respiratory distress syndrome (ARDS) were 10.9%, 4.3% and 18.4%, respectively. On meta-regression, ICU admission was predicted by raised leukocyte count ($p<0.0001$), raised alanine aminotransferase ($p=0.024$), raised aspartate transaminase ($p=0.0040$), elevated lactate dehydrogenase (LDH) ($p<0.0001$) and increased procalcitonin ($p<0.0001$). ARDS was predicted by elevated LDH ($p<0.0001$), while mortality was predicted by raised leukocyte count ($p=0.0005$) and elevated LDH ($p<0.0001$). Treatment with lopinavir-ritonavir showed no significant benefit in mortality and ARDS rates. Corticosteroids were associated with a higher rate of ARDS ($p=0.0003$).

Keywords: coronavirus; covid-19; severe; risk factor; treatment

Introduction

A pandemic of coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread from Asia to the rest of the world in the first three months of 2020. The consequences for human health, the global economy and normal functioning of society have been unprecedented.

COVID-19 causes infection in any age group, though severe disease is more common in older adults [1]. The clinical spectrum of disease ranges from asymptomatic or subclinical infections to organ dysfunction – shock, acute respiratory distress syndrome (ARDS), acute cardiac injury, and acute kidney injury (AKI) – and death [2]. As of May 2, 2020, there was a total of 3,421,226 confirmed cases globally. Of the 1,333,313 cases that had an outcome reached, 240,222 had resulted in mortality [3].

The growth curve of COVID-19 academic literature since the first report of this outbreak from Wuhan, Hubei Province, China in December 2019 has been exponential [13,131 publications found on the National Institutes of Health COVID-19 Portfolio and 8502 publications found on PubMed on May 2, 2020 using the search string ‘coronavirus disease 2019 OR SARS-CoV-2’]. However, systematic reviews which consolidate these findings remain scarce, with none focused on understanding the predictors for severe disease including the effects of different experimental antiviral and immune-modulatory treatments [4].

To address this gap in the literature, we conducted a systematic review, meta-analysis and meta-regression to 1) investigate the predictive value of laboratory investigations for severe disease and adverse outcomes, and 2) evaluate the efficacy of antivirals and corticosteroids for COVID-19.

Methods

This review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5].

Search strategy

A search string was developed to identify original research studies reporting clinical features and treatment outcomes of patients with COVID-19 [see Supplementary Table 1]. The search was applied to the following databases: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed. Searches were performed for each database on March 15, 2020. Limits were applied to the search to identify studies published after November 1, 2019 as the first case of novel coronavirus was only reported in December 2019.

Study selection

All titles and abstracts were screened independently by two reviewers (JJYZ and KSL) against a set of pre-defined eligibility criteria. Potentially eligible studies were selected for full-text analysis. Disagreements were resolved by consensus or appeal to a third senior reviewer (BEY). Agreement among the reviewers on study inclusion was evaluated using Cohen's kappa [6].

All original studies reporting the clinical characteristics (symptoms and signs, laboratory investigations and radiological findings) and treatment outcomes of patients with COVID-19 were included in our meta-analysis. Case reports and series with a sample size of <5 were excluded per recommendations by the Cochrane Statistical Methods Group and in accordance with methodologies of previously published meta-analyses [7-9]. Other exclusion

criteria included non-English articles, non-original research papers, laboratory-based and epidemiological studies with no clinical characteristics reported, as well as non-human research subjects [see Supplementary Table 2].

Risk of bias assessment

The quality of included studies was assessed using the Joanna Briggs Institute (JBI) checklist for prevalence studies and the JBI checklist for case series [10]. Full details are in Supplementary Tables 3 and 4. In summary, these tools rated the quality of selection, measurement and comparability for all studies and gave a score for prevalence studies (maximum of 9) and case series (maximum of 10). Two researchers (JJYZ and KSL) assessed the quality of all included studies and discussed discrepancies until consensus was reached.

Data Extraction and Outcome Measures

Data were extracted on the following variables: study details, sample size of study, method of diagnosis, age, gender, coexisting medical conditions, clinical symptoms, laboratory investigations, radiological findings, treatment details and patient outcomes.

Primary outcome measures were intensive care unit (ICU) admission rate, mortality rate and the event rate of ARDS. ICU admission was used as a surrogate marker for severe infection. Secondary outcome measures included other morbidities such as respiratory failure, septic shock, coagulopathy, acute cardiac injury, AKI and secondary infection, as well as length of hospital stay (LOS) and discharge rate at the point of study completion.

Statistical Analysis

To account for intra-study and inter-study variance, random effects models were used for meta-analyses of variables and end points [11]. Pooled proportions were computed with the inverse variance method using the variance-stabilizing Freeman-Tukey double arcsine transformation [12]. Confidence intervals (CI) for individual studies were calculated using the Wilson Score confidence interval method with continuity correction. The I^2 statistic was used to present between-study heterogeneity, where $I^2 \leq 30\%$, between 30% and 50%, between 50% and 75%, and $\geq 75\%$ were considered to indicate low, moderate, substantial, and considerable heterogeneity, respectively [13]. P values for the I^2 statistic were derived from the chi-square distribution of Cochran Q test. For pooling of means of numerical variables, we computed missing means and standard deviations (SDs) from medians, ranges (minimum to maximum) and interquartile ranges (IQRs) using the methods proposed by Hozo et al. and Wan et al [14, 15].

Summary-level meta-regression was performed using the mixed-effects model after computation of the SD of Freeman-Tukey double arcsine transformed proportions. Publication bias of studies was assessed using funnel plots, where an asymmetrical distribution of studies was suggestive of bias [16]. Quantitative analysis of funnel plot asymmetry was done using Egger's regression test, based on a weighted linear regression of the treatment effect (expressed as a Freeman-Tukey double arcsine transformed proportion) on its standard error [17]. The GRADE approach was used to evaluate the quality of evidence for each outcome [18].

All statistical analyses were performed using R software version 3.4.3 (R Foundation for Statistical Computing, 2016), with the package *meta* [19]. P-values less than 0.05 were considered statistically significant.

Results

Our search yielded 1481 unique publications. After screening of titles and abstracts, 109 publications were reviewed in full text. A total of 45 studies reporting 4203 patients met eligibility criteria for inclusion in our meta-analysis [see Supplementary Figure 1]. Reliability of study selection between observers was substantial at both the title and abstract screening stage (Cohen's $\kappa = 0.86$) and the full-text review stage (Cohen's $\kappa = 0.85$).

All included studies were non-randomized, retrospective observational studies. 42 studies reported data from China, with one each from Singapore, South Korea and Hong Kong. Details of included studies are reported in Supplementary Table 5. Of the 36 prevalence studies, 33 studies attained a full score of 9 on the JBI checklist for prevalence studies, two studies attained a score of 8 and one study attained a score of 7 [see Supplementary Table 3]. Of the nine case series, 7 studies attained a full score of 10, one study attained a score of 8 and one study attained a score of 7 [see Supplementary Table 4].

Of the total 4203 patients, 2797 were male (66.5%) and 1406 were female (33.5%). Supplementary Table 6 summarizes the demographics, medical comorbidities, clinical symptoms, laboratory investigations, radiological findings, treatment details and outcomes of all included patients. Pooled mean age was 45 years (95% CI: 35.5 – 54.5). The most common medical comorbidities were hypertension, cardiovascular disease and diabetes (16.4%, 12.1% and 9.8%, respectively). The most common clinical symptoms were fever, cough and dyspnea (80.5%, 58.3% and 23.8%, respectively). Definition of fever was specified in 9 studies [7 studies $\geq 37.3^{\circ}\text{C}$; 2 studies $\geq 37.5^{\circ}\text{C}$]. Pooled mean incubation period was 6.1 days (95% CI: 5.0 – 7.3). Pooled mean time from symptom onset to hospital admission was 7.2 days (5.5 – 8.9).

The most common blood abnormalities observed were elevated C-reactive protein (CRP) (59.4%), decreased albumin (58.6%), elevated lactate dehydrogenase (LDH) (51.7%) and lymphopenia (47.7%). The most common radiological abnormalities seen on chest computed tomography (CT) scan were bilateral infiltrates (80.8%), ground glass opacities (73.0%), interlobular septal thickening (46.3%), subpleural lines (45.5%) and consolidation (41.6%). In terms of treatment, type of antivirals used included combinations of oseltamivir, ganciclovir, lopinavir, ritonavir, ribavirin and arbidol. Type of antibiotics used comprised moxifloxacin, ceftriaxone and azithromycin.

Overall Outcomes

Table 1 summarizes the overall outcome findings. At the point of study completion, pooled ICU admission rate was 10.9% (95% CI: 4.5 – 19.3) [see Supplementary Figure 2]. Pooled mortality rate was 4.3% (95% CI: 1.0 – 9.1) [see Supplementary Figure 3]. ARDS was the most common complication, with a pooled event rate of 18.4% (95% CI: 7.4 – 32.4) [see Supplementary Figure 2]. Study heterogeneity was considerable for ICU admission, mortality and ARDS rates [Table 1]. In 16.2% of all patients (95% CI: 0.4 – 43.3), ARDS progressed to respiratory failure. The second and third most common complications were secondary infections (8.7% [95% CI: 4.9 – 13.3]) such as hospital-acquired or ventilator-associated pneumonia and acute cardiac injury (7.8% [95% CI: 1.2 – 18.2]), respectively. Among the studies that reported secondary infections, four specified the method of diagnosis. In all four of these studies, diagnosis required a positive bacterial culture, either from a lower respiratory tract specimen (including qualified sputum, endotracheal aspirate or bronchoalveolar lavage fluid) or from blood samples. Acute cardiac injury was defined consistently across studies as an elevated level of serum cardiac biomarkers (e.g. troponin I) above the 99th percentile upper reference limit, or new abnormalities demonstrated in electrocardiography and echocardiography.

Publication Bias

Funnel plots and Egger's regression test were done to assess for publication bias for ICU admission, mortality and ARDS rates. There was no evidence of publication bias for ICU admission ($p = 0.42$), mortality ($p = 0.41$) and ARDS ($p = 0.14$) [see Supplementary Figure 4].

GRADE Assessment

At baseline, the quality of evidence derived from a review of COVID-19 studies was assessed as low, owing to their observational nature. The quality of evidence for respiratory failure was rated down to very low for imprecision, due to the large confidence interval range and the relatively small sample size analyzed. Despite considerable study heterogeneity demonstrated by the I^2 values for most outcome measures, there was no rating down due to inconsistency, as the heterogeneity could likely be explained by differences in patient demographics, diagnostic criteria, treatment methods and management protocols given that COVID-19 is a newly emergent disease.

Risk Factors of ICU Admission, Mortality and ARDS

Meta-regression was performed to identify risk factors of ICU admission, ARDS and mortality [Table 2]. Fourteen studies with a total of 2153 patients reported ICU admission rates. ICU admission was predicted by raised leukocyte count ($p < 0.0001$), raised alanine aminotransferase (ALT) ($p = 0.024$), raised aspartate transaminase (AST) ($p = 0.0040$), elevated LDH ($p < 0.0001$) and increased procalcitonin ($p < 0.0001$) [Fig. 1]. ICU admission was not significantly associated with elevated creatine kinase (CK) ($p = 0.053$), decreased leukocyte count ($p = 0.29$), lymphopenia ($p = 0.44$), thrombocytopenia ($p = 0.80$), elevated D-dimer ($p = 0.41$), elevated creatinine ($p = 0.63$), and elevated CRP ($p = 0.88$).

ARDS was significantly predicted by elevated LDH ($p < 0.0001$) [Fig. 2], while mortality was predicted by raised leukocyte count ($p = 0.0005$) and elevated LDH ($p < 0.0001$) [Fig. 3].

Supplementary Table 7 summarizes all risk factors of ARDS, mortality and severe COVID-19 infection reported in the literature to date.

Efficacy of Lopinavir-Ritonavir Treatment

Subgroup analysis was performed according to reported antiviral treatment. Studies reporting use of lopinavir and ritonavir were grouped together and compared with studies that reported other antiviral combinations or did not specify the type of antivirals used. Eight studies reporting 633 patients used the combination of lopinavir and ritonavir (lopinavir-ritonavir group) and 13 studies reporting 2079 patients used other combinations of antivirals or did not specify the type of antiviral ('Others/Not specified' group). Other combinations included oseltamivir, ganciclovir, ribavirin and arbidol. Of these, 18 studies reported mortality rate and 12 studies reported the percentage of patients with ARDS.

Of all the patients where antiviral use was reported, the overall rate of mortality and ARDS was 5.7% and 20.2%, respectively. On subgroup analysis, the lopinavir-ritonavir treatment group had a lower rate of ARDS, though this difference was not statistically significant (15.6% versus 24.2 %, $p = 0.49$) [Fig. 4]. Mortality rate was comparable between the lopinavir-ritonavir group and the 'Others/Not specified' group (6.2% versus 5.5% respectively, $p = 0.93$) [see Supplementary Figure 5].

Efficacy of Corticosteroids

Subgroup analysis was performed for studies with the use of corticosteroids reported. Sixteen studies with a total of 2407 patients reported the use of corticosteroids. Pooled mortality rate in these patients was 7.2% (95% CI: 1.7 – 15.4) and pooled ARDS rate was 22.7% (95% CI: 9.9 – 38.6). Meta-regression demonstrated a significant association between corticosteroids use and higher rate of ARDS ($p = 0.0003$) [Fig. 5].

Discussion

Our meta-analysis provides an in-depth analysis of the key epidemiological features, clinical characteristics, laboratory investigations, radiological findings, treatment details and outcomes of COVID-19 from published literature. We identified elevated LDH as a significant predictive marker of ARDS, and found that both elevated leukocyte count and elevated LDH predict mortality. Treatment with the anti-retroviral drug lopinavir-ritonavir was not associated with significant benefit, while corticosteroids were associated with possible harm.

Early recognition of severe infection may allow early intervention with supportive measures and therapeutics and improve outcomes [20]. Our meta-regression identified five significant markers of ICU admission: raised leukocyte count, raised ALT and AST, in addition to elevated LDH and finally increased procalcitonin. While 10.7% of patients had a raised leukocyte count in our meta-analysis, the degree of leukocytosis was modest (pooled mean leukocyte count was $6.0 \times 10^9/L$). Raised ALT and AST in severe COVID-19 disease may be a result of liver damage caused by the direct binding of SARS-CoV-2 to angiotensin-converting enzyme 2 positive cholangiocytes [21]. In our analysis, LDH was the only marker that significantly predicted all three measured outcomes: ICU admission, ARDS and mortality. LDH is released from cells upon damage to their cytoplasmic membrane, and is not only a metabolic but also an immune surveillance prognostic biomarker [22, 23]. LDH increases the production of lactate, which leads to enhancement of immune-suppressive cells and inhibition of cytolytic cells [24]. These changes could weaken the immune response mounted against the viral infection, resulting in more severe disease in patients with elevated LDH. Increased procalcitonin may have been a marker of bacterial co-infection, thereby resulting in complications of COVID-19 disease and hence a higher rate of ICU admission in these patients [25]. Interestingly, lymphopenia was not found to be a significant predictor of ICU admission, mortality and ARDS in our meta-analysis. A possible explanation may be that we analyzed lymphopenia as a dichotomous variable without taking into account

the degree of lymphopenia i.e. the numerical value of lymphocyte count, which lies on a spectrum and could affect disease severity among patients with lymphopenia.

The results of randomized clinical trials of COVID-19 interventions are of critical importance as only weak evidence supports the currently available repurposed and novel antivirals [26]. Among the patients with antiviral use reported in our meta-analysis, overall rates of mortality, ICU admission and ARDS were 5.7%, 11.8% and 20.2%, respectively. We found no overall benefit from treatment with lopinavir-ritonavir, in line with a recent randomized controlled trial (RCT) of 199 patients by Cao et al. (published after our search was conducted) [27]. However, this trial demonstrated that lopinavir-ritonavir treatment granted a significant reduction in ICU length of stay in survivors. Further trials (NCT04252885 and NCT04307693) are in progress to assess the efficacy of both lopinavir and ritonavir in reducing the COVID-19 viral load, and we look forward to future developments to provide recommendations on the use of antiviral therapy [28, 29].

Severe COVID-19 is associated with a dysregulated host inflammatory response, suggesting immune modulators as an attractive treatment modality [30]. Corticosteroids were used during the SARS-CoV outbreak, however, in a meta-analysis only four studies provided conclusive data, and all four indicated possible harm [31, 32]. These harms included risks of prolonged viremia, corticosteroid-induced diabetes, avascular necrosis and psychosis [31, 33, 34]. Our meta-analysis suggested that the use of corticosteroids is associated with disease severity (ICU admission) and higher ARDS rates. It is not clear if this effect is a consequence of corticosteroid treatment, or confounding by indication bias where sicker patients are more likely to receive corticosteroids. An RCT of corticosteroids in severe respiratory viral infections has long been called for, and at least one clinical trial in COVID-19 (NCT04244591) is ongoing [35].

SARS-CoV-2-induced pneumonia is marked by a cytokine storm – hyperactivation of effector T cells and excessive production of inflammatory cytokines, particularly interleukin-6 (IL-6) [36]. Blockade of IL-6 function using tocilizumab, a specific monoclonal antibody against its receptor appears to be useful in alleviating hyperinflammation symptoms in severe cases [37, 38]. Selective Janus kinase-signal transducer and activator of transcription (JAK-STAT) inhibitors such as baricitinib may also be beneficial, though clinical trials are required and any benefit is likely to be greatest in combination with an effective antiviral [39].

There are several limitations to our study. First, only studies published in English were included which may have introduced selection bias. Unpublished materials (such as recently completed studies) were also excluded, which might have affected the conclusions drawn. Second, the results may not be generalizable to health care systems outside Asia as no studies from Europe or the United States were available for inclusion in our review at the time of the literature search. Additionally, all included studies were observational. Clinical parameters were often not clearly defined and clinical follow-up time varied. Finally, there was heterogeneity in the range of symptoms and comorbidities recorded by different studies due to the lack of objective measurements.

Conclusion

To the best of our knowledge, this is the first systematic review and meta-analysis of COVID-19 to describe specific laboratory predictors of severe disease and adverse outcomes. Our study is also the first meta-analysis to evaluate the efficacy of antivirals and corticosteroids. Careful attention should be given to the management of patients with raised leukocyte count, raised ALT and AST, elevated LDH, increased procalcitonin and raised leukocyte count as these factors predict ICU admission, mortality and ARDS. In terms of treatment efficacy, the use of corticosteroids in COVID-19 patients is significantly associated with higher rates of ARDS. Compared to other antivirals, the use of lopinavir and ritonavir is non-superior in terms of lowering mortality rate. Further prospective studies are vital to clarify our findings.

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Conflicts of Interest

All authors have no potential conflicts of interest to disclose.

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Table 1. Pooled outcomes of included patients.

Outcome	No. of studies reporting variable	No. of patients analyzed	Pooled mean value or percentage of patients (95% CI)	I ² (%)	P value of I ²	Quality of Evidence (GRADE)
ICU Admission	14	2153	10.9 (4.5 – 19.3)	94.9	<0.0001	Low
Mortality	23	2921	4.3 (1.0 – 9.1)	94.1	<0.0001	Low
Complications						
ARDS	13	2221	18.4 (7.4 – 32.4)	97.7	<0.0001	Low
Respiratory failure	8	552	16.2 (0.4 – 43.3)	97.2	<0.0001	Very Low
Shock	8	1738	4.3 (0.3 – 11.3)	93.6	<0.0001	Low
Coagulopathy	3	1299	3.3 (0.0 – 27.7)	98.3	<0.0001	Low
Acute cardiac injury	7	592	5.5 (1.1 – 12.2)	90.6	<0.0001	Low
Acute kidney injury	7	592	8.7 (4.9 – 13.3)	90.6	<0.0001	Low
Secondary	11	1958		93.8	<0.0001	Low

infection	8	588		55.7	0.0270	Low
Length of hospital stay (days)	6	1531	12.2 (10.9 – 13.4)	94.3	<0.0001	Low
Duration of viral shedding (days)	5	261	14.8 (11.5 – 18.2)	96.0	<0.0001	Low
Discharged	22	2922	37.4 (23.6 – 52.3)	98.1	<0.0001	Low

Table 2. Summary of laboratory predictors of intensive care unit admission, acute respiratory distress syndrome and mortality identified on meta-regression.

Outcome	No. of studies reporting outcome	Risk Factor	P value
ICU Admission	14	Leukocytosis	< 0.0001
		Raised ALT	0.0235
		Raised AST	0.0040
		Elevated LDH	< 0.0001
		Increased procalcitonin	< 0.0001
ARDS	13	Elevated LDH	< 0.0001
Mortality	23	Leukocytosis	0.0005
		Elevated LDH	< 0.0001

ICU, intensive care unit. ALT, alanine aminotransferase. AST, aspartate aminotransferase.

LDH, lactate dehydrogenase. ARDS, acute respiratory distress syndrome.

Figure Legends

Figure 1. Bubble plot for meta-regression of transformed ICU admission rate against (A) percentage of patients with leukocytosis, (B) percentage of patients with raised alanine aminotransferase (ALT), (C) percentage of patients with raised aspartate aminotransferase (AST), (D) percentage of patients with elevated lactate dehydrogenase (LDH) and (E) percentage of patients with increased procalcitonin in each study.

Figure 2. Bubble plot for meta-regression of transformed proportion of acute respiratory distress syndrome (ARDS) against percentage of patients with elevated lactate dehydrogenase (LDH) in each study.

Figure 3. Bubble plot for meta-regression of transformed mortality rate against (A) percentage of patients with leucocytosis and (B) percentage of patients with elevated lactate dehydrogenase (LDH) in each study.

Figure 4. Forest plot for subgroup analysis of ARDS by type of antiviral used. The event rate is the incidence of ARDS in lopinavir and ritonavir recipients (top of figure) versus recipients of other/non-specified antivirals (bottom of figure).

Figure 5. Bubble plot for meta-regression of transformed acute respiratory distress syndrome (ARDS) rate against percentage of patients on corticosteroids in each study.

Figure 1

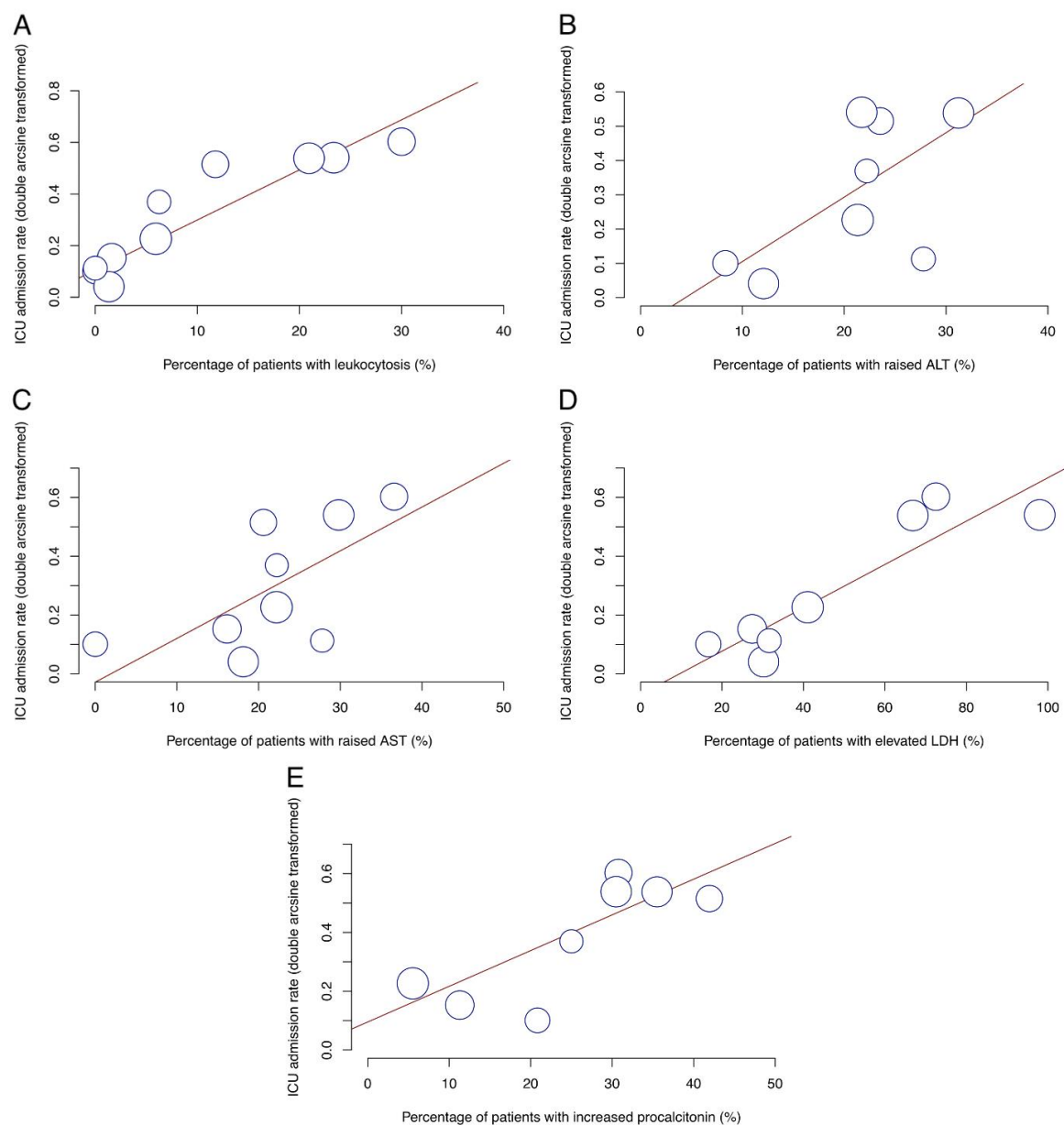


Figure 2

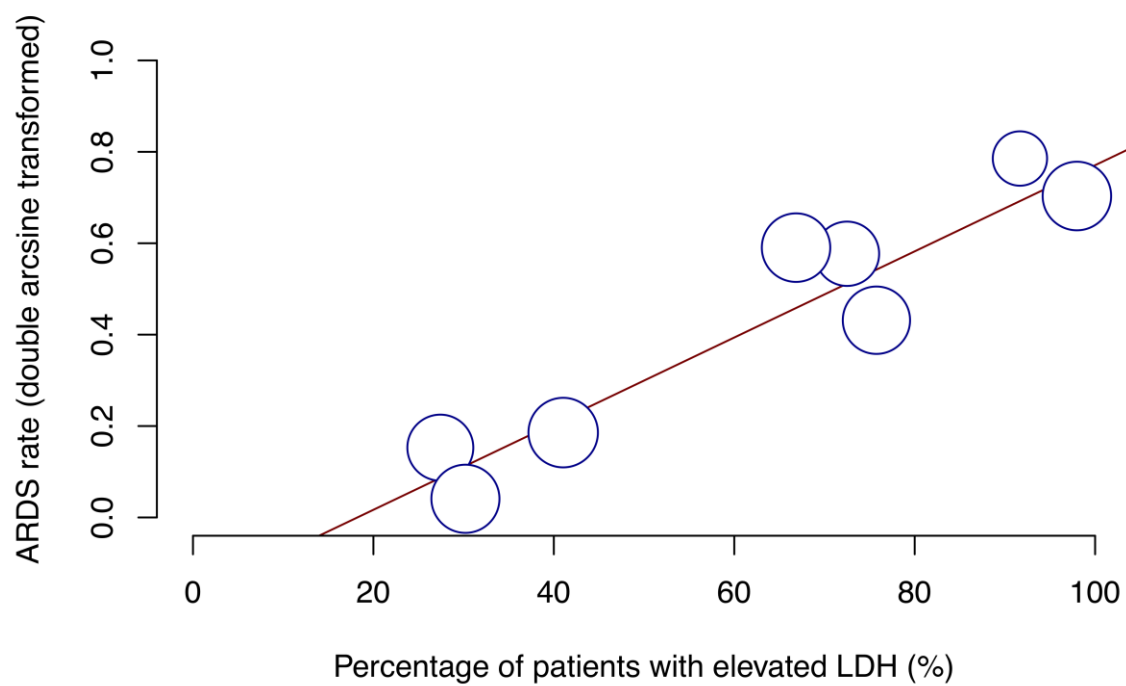


Figure 3

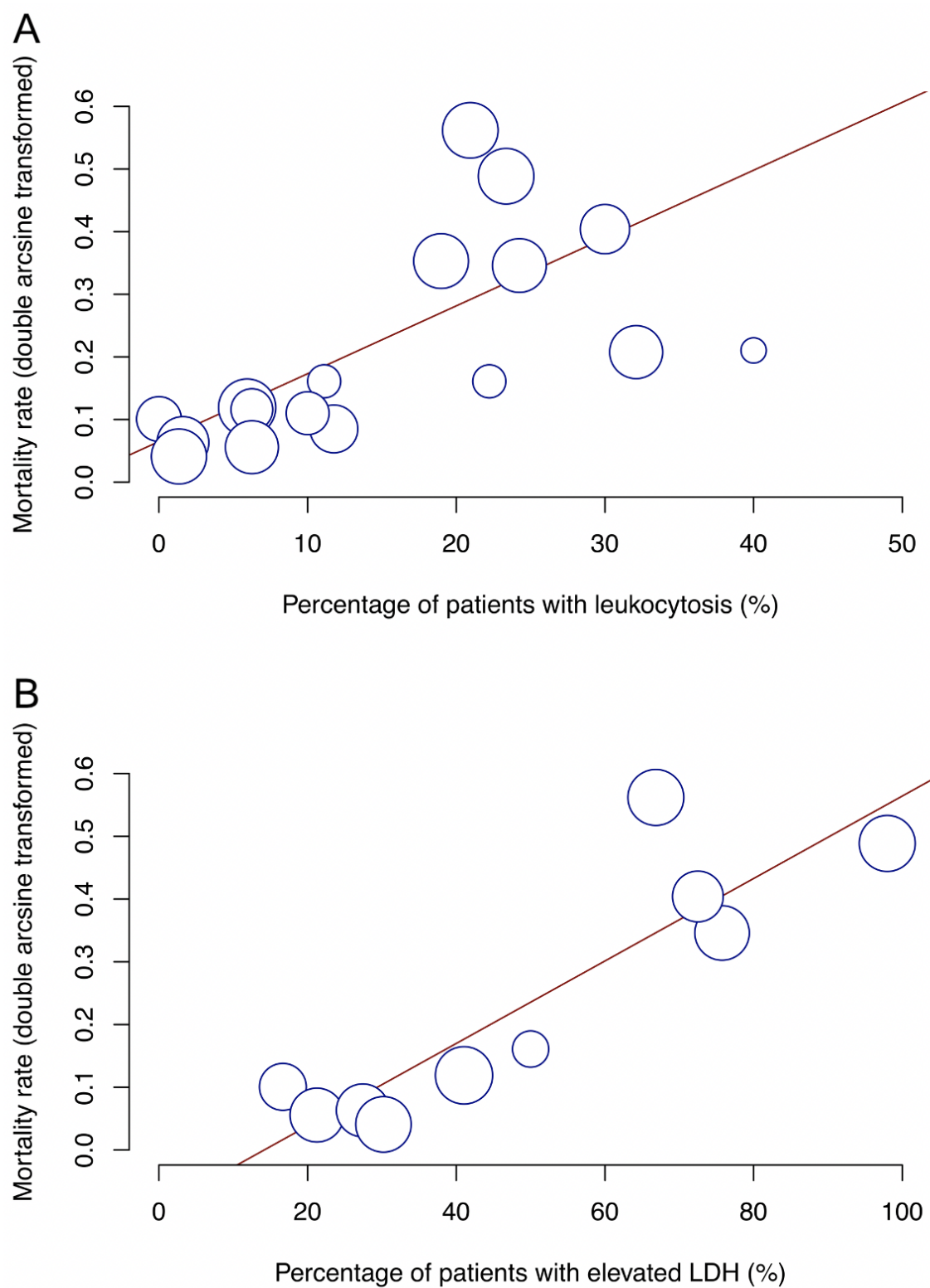


Figure 4

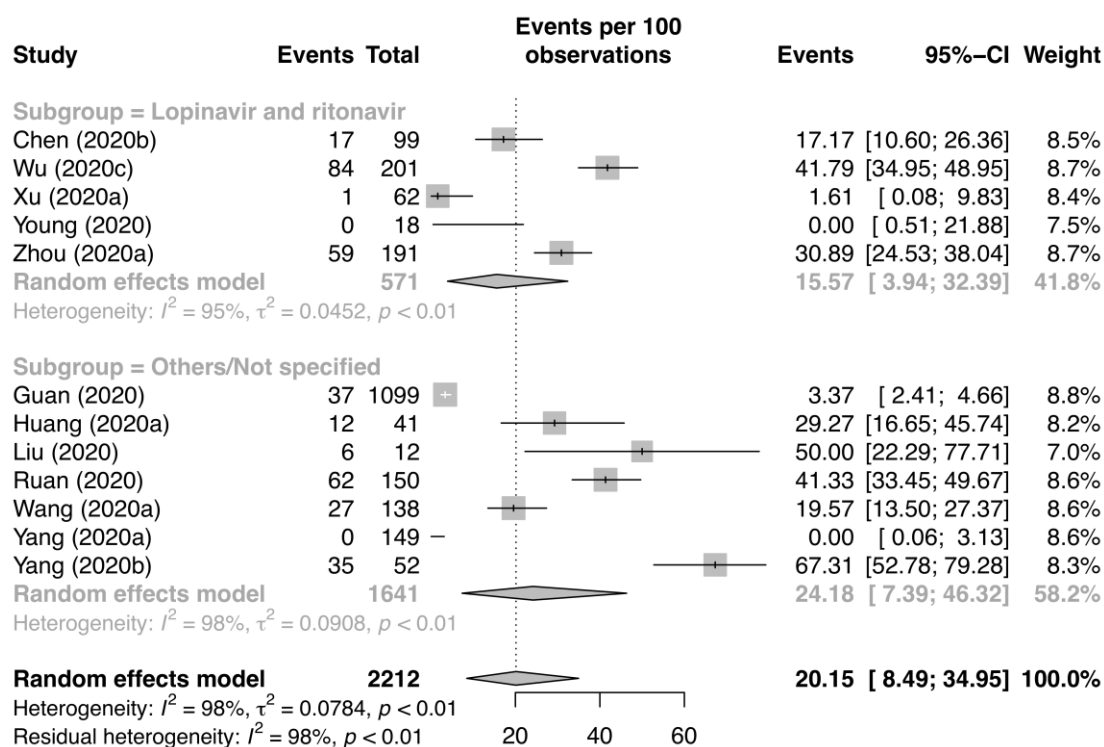
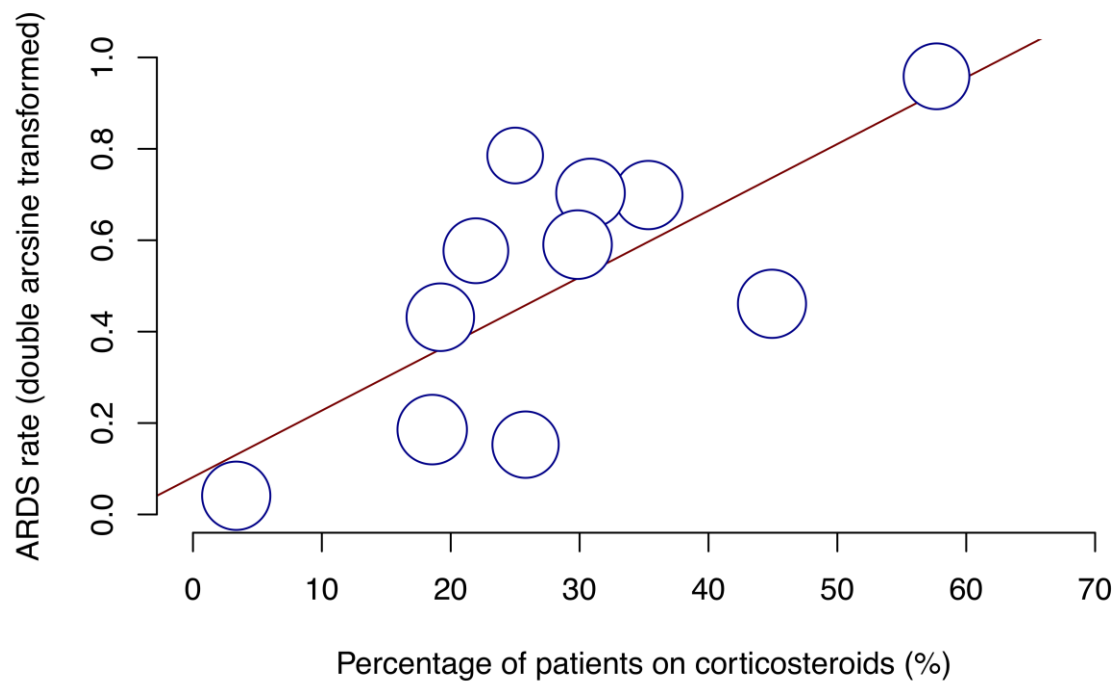


Figure 5

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Accepted