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Research Article

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Severity and Mortality in Covid-19 With Hepatitis B Co-Infection A Systematic Review and Meta-Analysis

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Abstract

This systematic review and meta-analysis investigate the severity and mortality in COVID-19 patients co-infected with Hepatitis B Virus (HBV). Utilizing established databases and adhering to PRISMA guidelines, 15 studies were included after a rigorous selection and data extraction process, with quality assessed using the Newcastle–Ottawa Scale (NOS). Statistical analysis was conducted using Review Manager (RevMan) software. The findings indicate a significantly higher risk of severe clinical outcomes and mortality in COVID-19 patients with HBV co-infection compared to those without HBV. Among patients with both HBV and COVID-19, 30.2% developed severe clinical outcomes, compared to 19.5% in COVID-19 patients without HBV. Mortality rates were also higher in the co-infected group (4.9%) compared to those with only COVID-19 (3.4%). The study notes considerable heterogeneity among the included studies, as indicated by high I2 values. These results align with previous findings on the impact of chronic liver diseases on COVID-19 outcomes but contrast with some studies suggesting a potential protective effect of HBV. The analysis also considers the complexities of managing COVID-19 in HBV patients, particularly the risks associated with corticosteroid therapy and HBV reactivation, while acknowledging limitations such as variability in methodologies and potential publication biases. The study underscores the heightened severity and mortality risks for COVID-19 patients with HBV co-infection, emphasizing the need for tailored management strategies and further research into the mechanisms and optimal treatment protocols for this patient population.

1. Introduction

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has posed significant challenges to global health, revealing the critical need to understand how comorbidities influence the course and outcome of the infection [1]. Among various comorbid conditions, hepatitis B virus (HBV) infection stands out due to its widespread prevalence and potential impact on the immune system and disease progression [2]. Hepatitis B, a major cause of chronic liver disease worldwide, affects approximately 257 million people, presenting a significant public health concern [2]. The intersection of COVID-19 and HBV infection is particularly concerning, as it may exacerbate clinical outcomes due to the combined effects on the liver and overall health.

The interaction between viral respiratory infections and chronic liver diseases has been a subject of study in the past [3]. Research has shown that individuals with chronic liver diseases, including HBV, are at an increased risk of severe outcomes when infected with respiratory viruses like influenza

[3]. This prior knowledge raises concerns about the potential implications of HBV co-infection in the context of COVID-19. The pathophysiological mechanisms underlying this increased risk are not fully understood, but they are thought to involve a complex interplay of immune dysregulation, pre-existing liver damage, and the added strain of a viral infection [4]. This study aimed at exploring the severity and survival outcomes in COVID-19 patients with HBV co-infection. Such an analysis is crucial for several reasons. First, it contributes to a deeper understanding of how HBV co-infection affects COVID-19 severity and mortality, which is essential for managing these patients effectively. Second, it adds to the growing body of knowledge regarding the impact of co-existing comorbidities on COVID-19, which is vital for developing comprehensive treatment strategies. Lastly, insights gained from this analysis could have broader implications for managing viral co-infections in general, particularly in populations with a high prevalence of HBV.

2. Method

This systematic review and meta-analysis were meticulously structured to evaluate the severity and survival outcomes in COVID-19 patients with hepatitis B virus (HBV) co-infection. Our study was grounded in the principles outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a thorough, systematic, and transparent approach.

2.1 Search Strategy

We conducted a comprehensive search across several established databases PubMed, Embase, and the Cochrane Library. The objective was to collate a wide array of studies focusing on COVID-19 in the context of HBV co-infection. Our search strategy was formulated using a combination of Medical Subject Headings (MeSH) and specific keywords, tailored to capture studies pertaining to "Hepatitis B Virus" and "COVID-19." This meticulous approach was designed to encompass a broad spectrum of relevant research articles, maximizing the inclusivity of our study selection.

2.2 Study Inclusion and Exclusion

We set specific criteria for the inclusion of studies in our analysis. Eligible studies were those that diagnosed patients with COVID-19, compared COVID-19 patients with and without HBV co-infection, and reported on clinical outcomes such as severity (including indicators like ICU admission and mechanical ventilation) and mortality. Our exclusion criteria were focused on omitting studies that exclusively dealt with children, pregnant women, or distinct patient subgroups. Furthermore, we excluded non-empirical studies such as editorials, guidelines, narrative reviews, and case reports to ensure a focus on original research findings.

2.3 Study Selection and Data Extraction

The initial screening of identified studies was independently carried out by two researchers, with any conflicts resolved through consultation with a third senior researcher. This dual-reviewer approach ensured a thorough and unbiased selection process. The same researchers were responsible for meticulously extracting relevant data from the included studies, ensuring a consistent and detailed approach to data handling.

2.4 Quality Assessment

We employed the Newcastle–Ottawa Scale (NOS) for the assessment of study quality. This scale facilitated a nuanced evaluation, assigning each study a score that reflected its perceived risk of bias. The scoring ranged from 0, indicative of high risk, to 9, suggestive of low risk. In instances of discrepancy in quality assessment, we sought the input of an additional researcher to reach a consensus.

2.6 Statistical Analysis

The statistical analysis was conducted using Review Manager (RevMan) Web software. We evaluated the heterogeneity of the included studies using the I2 statistic, categorizing the heterogeneity as mild ($I2 < 50\%$), moderate ($50\% \leq I2 < 75\%$), or significant ($I2 \geq 75\%$). To compute the summary effect sizes and odds ratios (OR) with 95% confidence intervals (95%CI), we applied random-effects models. This approach was chosen to better accommodate the anticipated variability among the included studies. We set the threshold for statistical significance at a P value of less than 0.05.

3. Results

• Study Selection

The search initially identified 2,540 articles. After deduplication and screening, 42 articles were assessed in full text, resulting in 15 articles being included in the final analysis. For detailed methodology, see PRISMA chart (Figure 1).

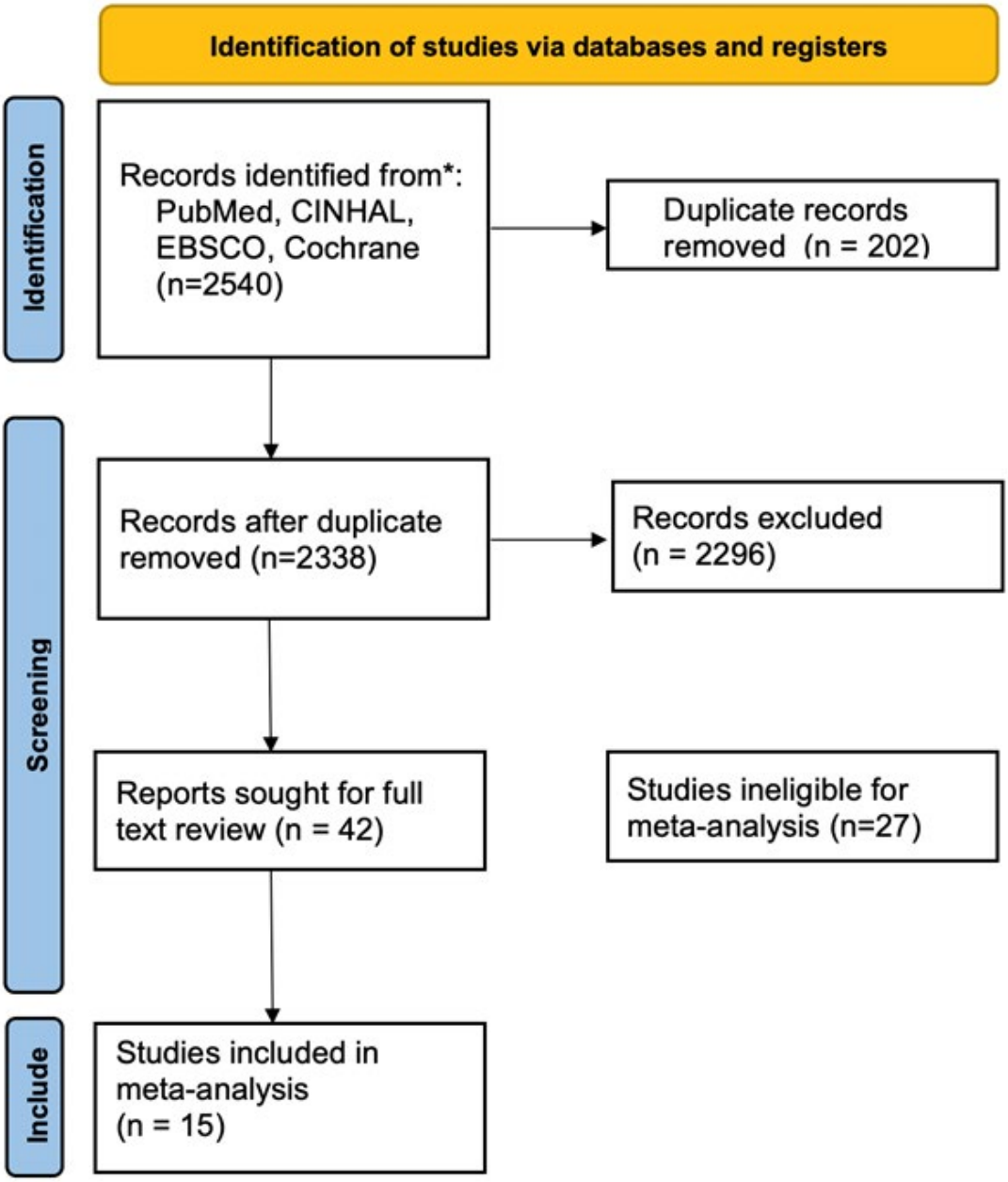


Figure 1: Study Characteristics and Comparative Analysis

Our research encompasses a broad spectrum of studies, summarized in Table 1 and Table 2. These tables collectively offer a comprehensive view of the research landscape and the impact of HBV on clinical outcomes.

Author	Year	Sample Size	NOS	Male (%)
Adali [5]	2021	231	Medium	66
Bekçibaşı [6]	2021	156	High	47
Chen L [7]	2020	326	Medium	51
Chen X [8]	2020	123	Medium	41
Choe [9]	2022	19160	Medium	47
Ding [10]	2021	2073	High	49
Ji [11]	2020	140	High	58
Kang [12]	2021	7723	High	Not mentioned
Liu [13]	2020	71	High	62
Liu [14]	2021	106	Medium	57

Wang [15]	2022	436	Medium	60
Wu [16]	2021	620	Medium	51
Yang [17]	2022	2899	High	51
Yip [18]	2021	5639	High	49
Yu [19]	2021	67	High	52

Table 1: Study characteristics table

Author	Year	Severe Clinical Outcome in	Total Patients with HBV	Severe Clinical Outcome in Non-HBV	Total Patients without HBV
Adali [5]	2021	6	77	15	154
Bekçibaşı [6]	2021	1	20	46	136
Chen L [7]	2020	2	20	27	306
Chen X [8]	2020	9	15	29	108
Choe [9]	2022	315	675	5237	18485
Ding [10]	2021	8	134	192	1939
Ji [11]	2020	0	7	1	133
Kang [12]	2021	38	267	679	7456
Liu [13]	2020	8	20	25	51
Liu [14]	2021	27	50	31	56
Wang [15]	2022	43	109	50	327
Wu [16]	2021	23	70	98	550
Yang [17]	2022	331	608	648	2291
Yip [18]	2021	29	712	109	4927
Yu [19]	2021	4	7	25	60

Table 2: Comparative Analysis of Severe Clinical Outcomes in HBV and Non-HBV Patients

3.1 Impact of HBV on Severe Clinical Outcomes in COVID-19

Total 15 studies explore the complex relationship between HBV infection and the severity of clinical outcomes in COVID-19 patients. The analysis indicates that patients with concurrent HBV and COVID-19 infection face a significantly higher risk of severe clinical outcomes compared to those without HBV. The odds ratio was found to be 1.72 (95% CI 1.30-2.26), denoting a notable increase in risk. Among 2,791 patients with both HBV and COVID-19, 844 (30.2%) developed severe clinical outcomes. In comparison, among 36,979 COVID-19 patients without HBV, 7,212 (19.5%) experienced severe outcomes, highlighting the increased risk associated with HBV co-infection. Combined I^2 value of studies were 75%. This high I^2 value suggests a considerable degree of heterogeneity among the studies. For visual representation, refere to the Figure 2.

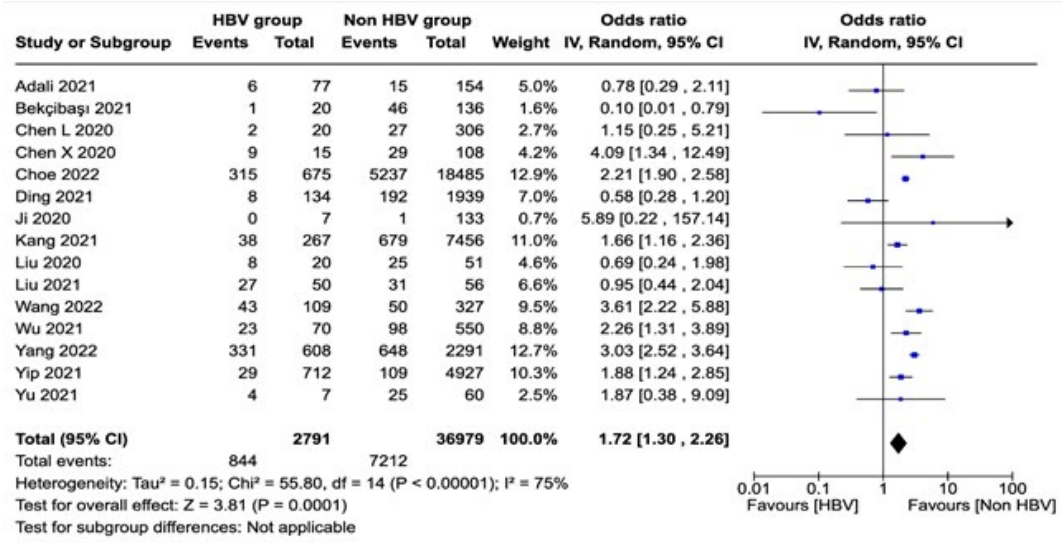
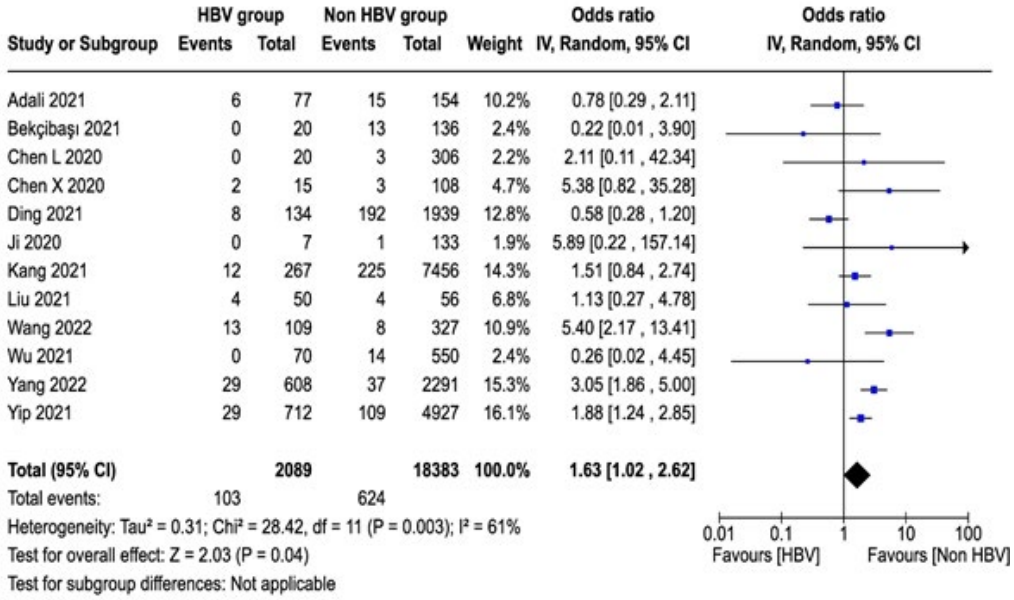


Figure 2: Mortality Analysis in HBV and COVID-19 Patients

Among 15 studies, 12 studies examined mortality rates in patients with HBV and COVID-19 compared to those with only COVID-19. Among 2,089 patients with both HBV and COVID-19, 103 (4.9%) passed away. Conversely, of the 18,383 patients with only COVID-19, 624 (3.4%) passed away. These findings suggest a higher mortality rate among patients co-infected with HBV and COVID-19. The statistical analysis showed an I^2 value of 61%, indicating a moderate level of heterogeneity. For more details, refer to the Figure 3.



4. Discussion

Our systematic review and meta-analysis have provided critical insights into the severity and mortality of COVID-19 in patients with concurrent hepatitis B (HBV) infection, revealing a complex interplay with significant clinical implications. Our findings indicate a notably higher in-hospital severity (30.2% vs. 19.5%) and mortality rate (4.9% vs. 3.4%) in COVID-19 patients with HBV compared to those without HBV, highlighting an odds ratio for severe outcomes of 1.72 and mortality of 1.63. In comparison to existing literature, our results align with the findings of Kovalic et al, which also observed an increased severity in COVID-19 infection among patients with chronic liver disease (CLD), though our study specifically focuses on HBV co-infection [20]. This similarity underscores the broader impact of liver diseases on COVID-19 outcomes. However, our study presents contrasts to other research in the field. Notably, He et al suggested a lower incidence of intensive care unit admission or death in COVID-19 patients with pre-existing HBV infection, proposing a potential protective effect mediated by host immune responses [21]. This apparent contradiction could be attributed to differences in study populations, methodologies, or even the stages of COVID-19 treatment protocols during the study periods. The corticosteroid therapy could be an independent risk factor for 28-day mortality in COVID-19 patients [22]. This aligns with our observation of increased severity and mortality in HBV co-infected patients, potentially implicating corticosteroid therapy in exacerbating liver-related complications in these patients. Our analysis also brings to light the complexity of managing COVID-19 in patients with HBV co-infection. The risk of HBV reactivation is a significant consideration, especially when treating severe COVID-19 patients with immunosuppressive drugs [13]. This risk is further complicated by accelerated progression of liver injury in viral co-infections, including HBV and COVID-19 [12,23].

Despite these insights, our study is not without limitations. The variability in methodologies of the included studies and potential publication biases may affect the generalizability of our findings. Furthermore, the evolving nature of COVID-19 treatment protocols and geographic variability in healthcare settings could influence patient outcomes. Future research should focus on a longitudinal assessment of the impact of HBV on COVID-19 outcomes, exploring the molecular mechanisms underlying the interaction between HBV and SARS-CoV-2, and investigating the role of specific treatments, such as corticosteroids, in the context of HBV co-infection.

5. Conclusion

Our systematic review and meta-analysis underscore the need for tailored management strategies for COVID-19 patients with concurrent HBV infection. These findings highlight increased severity and mortality risks, calling for further research into the underlying mechanisms and optimal treatment protocols for this patient population.

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