

Systematic Review in Internal Medicine and COVID-19

# A systematic review and meta-analysis of the association between galectin-3 levels and clinical outcomes in COVID-19 patients

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## Abstract

**Introduction:** Galectin-3 is a  $\beta$ -galactoside-binding lectin with several roles in the immune-inflammatory response. The aim of this systematic review and meta-analysis was to explain the prognostic value of Galectin-3 on COVID-19 severity and mortality from the existing literature.

**Methods:** PubMed/MEDLINE, EMBASE, SCOPUS, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were surveyed up to November 10, 2023, for studies reporting data on Galectin-3 levels and the severity and mortality of patients with COVID-19. We performed frequentist random-effects network meta-analysis and presented the standard mean difference (SMD) and 95% confidence interval (CI).

**Results:** Galectin-3 levels among patients with and without COVID-19 varied with the following values:  $15.73 \pm 13.03$  vs.  $8.72 \pm 5.82$  pg/mL, respectively (SMD = 2.59; 95%CI: 1.52 to 3.67;  $p < 0.001$ ). Galectin-3 levels were also statistically different between COVID-19 patients who were severe and those who were not ( $18.83 \pm 15.5$  pg/mL vs.  $12.43 \pm 10.29$  pg/mL; SMD = 2.64; 95%CI: 1.45 to 3.83;  $p < 0.001$ ), as well as between COVID-19 patients who survived and those who died ( $6.24 \pm 6.74$  pg/mL vs.  $13.72 \pm 15.92$  pg/mL; SMD = -1.79; 95%CI: -2.78 to -0.80;  $p < 0.001$ ).

**Discussion:** Galectin-3 seems to be a useful predictive biomarker of COVID-19 outcomes and needs further evaluation.

**Take-home message:** This meta-analysis found that Galectin-3 levels are significantly higher in COVID-19 patients and correlate with disease severity and mortality. This suggests that galectin-3 could be a valuable biomarker for predicting COVID-19 outcomes, warranting further investigation for clinical application.

**Keywords:** Biomarker; COVID-19; Coronavirus disease 2019; endothelial cells; Galectin-3; Gal-3; mortality; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2.

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## INTRODUCTION

The global health community continues to prioritize coronavirus disease 2019 (COVID-19) as its severity can fluctuate and pose a significant risk to patients who require hospitalization [1, 2]. Individuals experiencing severe manifestations of COVID-19 demonstrate altered responses to infection, fluctuations in immunological cytokine concentrations, diminished lymphocyte count,

extensive inflammation, compromised endothelial cell functionality, excessive blood coagulation, and lung tissue injury [3–5]. In this specific context, the evaluation of indicators related to severe infection holds importance as it facilitates the decision making on the basis of clinical prognosis [6]. Furthermore, alongside the presence of hyperinflammation, it was noted earlier in the pandemic that individuals afflicted with COVID-19 exhibited an elevated propensity for thrombotic events and thromboembolism [7,8]. COVID-19-related coagulopathy encompasses various pathophysiological mechanisms, including but not limited to endothelial dysfunction, platelet hyperreactivity, neutrophil extracellular traps, and complement system activation [9,10]. The pathophysiology of COVID-19 involves the participation of various thrombogenicity markers, such as those associated with platelet activation, coagulation, and fibrinolysis [11–13]. Therefore, identification of predictive biomarkers for the purpose of categorizing a patient's condition holds potential value in terms of facilitating in-hospital care and optimizing treatment strategies for high-risk patients.

Galectin-3, a constituent of the galectin family, is a protein that binds to carbohydrates and is localized on the cellular membranes of heart, Kidney, blood vessels, and macrophages. Galectins are a class of lectins that exhibit a high affinity for  $\beta$ -galactoside-containing molecules. They are ubiquitously expressed and are involved in regulating intercellular and extracellular matrix interactions in various organisms. Furthermore, galectins play a pivotal role in the processes of inflammation and fibrosis [14]. It was also shown that galectin-3 plays a key role in activating platelets and causing thrombi in patients [15]. Galectins play several important roles in biology, including controlling immune cell activity, helping tissues grow back, and various developmental processes [16]. Furthermore, an increased concentration of galectin-3 was found to be correlated with the presence of interstitial lung abnormalities and demonstrated a potential involvement in the initial phases of pulmonary fibrosis as well as in other pulmonary diseases [17, 18]. The secretion of this substance is primarily observed in macrophages, endothelial cells, and epithelial cells. Galectin-3 plays a pivotal role in viral infections and is implicated in the induction of interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor-alpha secretion [19,20]. In this background, this systematic review and meta-analysis aims to synthesize an evidence to explain the prognostic value of Galectin-3 on COVID-19 severity and mortality.

## **METHODS**

### ***Protocol and registration***

This review and meta-analysis were performed using the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [21]. This study was reported in the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration no.: CRD42023480215).

### ***Search strategy and study selection***

A literature search for all relevant studies was performed in PubMed/MEDLINE, EMBASE, SCOPUS, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. Studies comparing Galectin-3 levels among different COVID-19 patients' statuses (severe vs. non-severe and survive vs. deceased) were selected for this systematic review and meta-analysis. A distinct and efficient search methodology was utilized for each individual database. For this purpose, we search terms: "SARS-CoV-2" OR "COVID-19" OR "novel coronavirus" OR "severe acute respiratory syndrome coronavirus 2" OR "nCOV" and "Galectin-3" OR "Galectin 3" OR "Gal-3". We expanded our search efforts by utilizing the "related articles" feature and conducting an extensive exploration of unpublished literature. This involved examining the reference lists of all included studies and existing traditional systematic reviews. Additionally, we explored gray literature sources such as Google Scholar to gather information on the effects of SARS-CoV-2 infection on OHCA outcomes. Endnote (X7 for Windows, Clarivate Analytics, Philadelphia, PA, USA) was used to consolidate search results, and duplicates were deleted. To streamline the process, duplicate results were first eliminated. Subsequently, two authors independently assessed the relevance of the remaining articles based on their abstracts. The investigators then thoroughly reviewed those articles that met the predetermined criteria. Articles meeting the criteria were included in the study. The final selection of

studies was determined by unanimous agreement among all investigators, with any disagreements resolved through consensus. Finally, the full texts of the remaining articles were evaluated in accordance with the established inclusion and exclusion criteria. The initial searches were conducted on September 11, 2023, and were repeated on November 10, 2023 to locate newly published studies.

### Eligibility criteria

We included all research articles in adult patients diagnosed with COVID-19 with information on galectin-3 levels and clinical grouping or outcome of the clinically validated definition of mortality, or COVID-19 severity. The following types of articles were excluded: non-English articles, duplicate publications, or articles other than original research (e.g., editorials, commentaries, letters to editors, review articles, case reports, or series). Please see the figure 1 below that explains the detailed inclusion criteria.

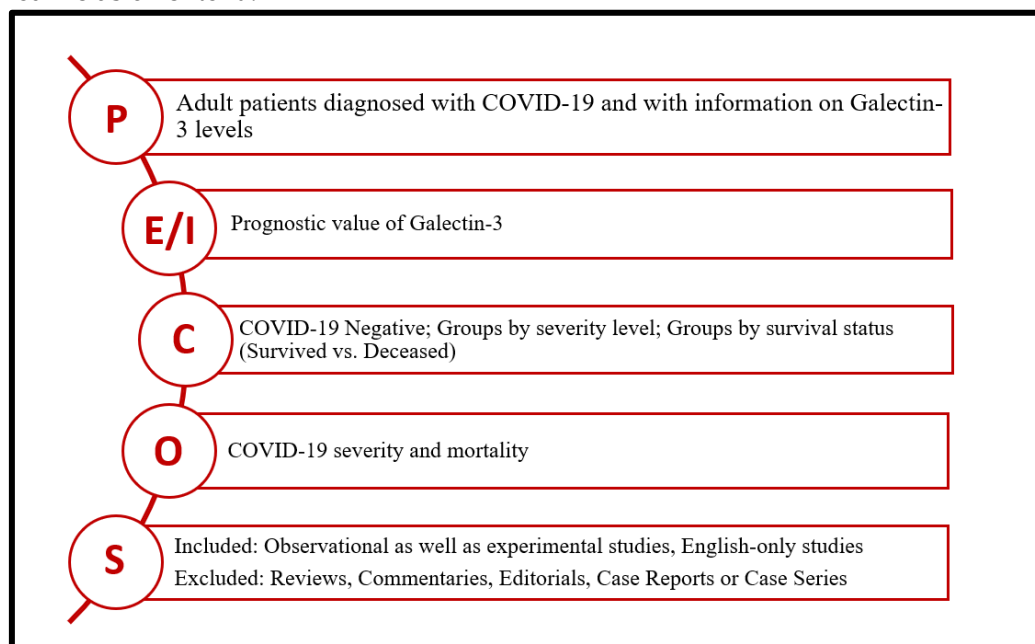


Figure 1. PECOS Framework of the study.

### Data extraction

K.D. and M.P. independently extracted the data from each study using an Excel sheet with a customized format. All authors reached a consensus to resolve the differences between the two independent authors. The extracted data included: author names, country, year of publication, study design, sample size, mean age, male gender percentage, body mass index (BMI), and Galectin-3 levels. Finally, data were then imported for analysis in Review Manager version 5.4 (Cochrane Collaboration, Copenhagen, Denmark).

### Quality of the included studies

Two authors (K.D. and F.C.) independently evaluated methodological quality and bias risk for publications that satisfied the inclusion criteria. The quality assessment of the included studies was done using the Newcastle-Ottawa Scale (NOS). NOS judged the study's quality using an eight-item scale divided into three areas: the choice of participants, the ability to compare, and the ability to find the desired outcome [22]. The NOS for cross-sectional and case-control studies has a maximum overall score of nine and a minimum score of zero. Studies with NOS scores of 7 or more were considered high-quality. A third author reviewed and resolved any discrepancies in the NOS.

### Data synthesis and statistical analysis

A meta-analysis was performed if two or more of the included studies reported data on the outcomes of interest. Data processing and statistical analysis were conducted using Review Manager. The incidence of dichotomous data was calculated using the odds ratio (OR) with a 95% CI and analyzed using the Mantel-Haenszel technique. The standard mean difference (SMD) with a 95%

confidence interval (CI) was used to represent continuous outcomes. If the median was reported, the published methods by Hozo et al. were used to estimate the mean [23]. A conventional pairwise meta-analysis was conducted using the standardized mean difference. Heterogeneity was tested by using Cochran's Q statistic, which was calculated by means of H and I-squared ( $I^2$ ) indices. The  $I^2$  statistical measure was used to describe the percentage of variation across the included studies due to heterogeneity. Conventionally,  $I^2$  values of 0–25% indicate low heterogeneity, 26–75% indicate moderate heterogeneity, and 76–100% indicate substantial heterogeneity [24]. Random effects models were used in all analyses, regardless of heterogeneity, as evidence suggests that they provide more robust outcome measures compared to the fixed effects models [25]. Publication bias was checked with a funnel plot, and the objective diagnostic test was conducted with Egger's correlation and Begg's regression tests. Assessment of publication bias of the rest of the pooled estimates was not possible because of an insufficient number of studies, since at least 10 studies are required to assess publication bias [26]. The p-values were two-tailed, and statistical significance was set at 0.05. Additionally, a sensitivity analysis by leave-one-out was performed to investigate the impact of each study on the overall pooled estimate. This systematic review and meta-analysis were conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [24].

### ***Search strategy***

Four independent reviewers (M.P., A.H., A.B., and M.M.) searched four main electronic databases (Web of Science, PubMed, Scopus, and the Cochrane Central Register of Controlled Trials) from January 1st, 2020 to September 2nd, 2022, to find papers investigating the prognostic significance of interleukin-7 in COVID-19-hospitalized adults. Google Scholar was used in addition to the online database search. For each source, a unique and suitable search approach was used. We were using the following search terms: "interleukin 7" OR "IL-7" AND "SARS-CoV-2" OR "COVID-19" OR "novel coronavirus". The EndNote application was used to handle the search results (version X7; Thomson Reuters). References for related papers were also examined.

### ***Study selection***

Original studies that reported IL-7 levels in COVID-19 patients on at least one or more of the following outcomes, like COVID-19 severity, were included. Original English-language articles were included. The exclusion criteria for the meta-analysis were as follows: (1) studies containing pediatric patients' data; (2) case reports, editorials, conference papers, and reviews; (3) studies published in languages other than English; and (4) studies without the research parameters needed for meta-analysis. Two reviewers (M.M. and M.P.) independently looked at the search criteria and compared the titles and abstracts of the papers found by the databases. Following that, the same reviewers obtained the complete texts of all potentially pertinent papers and independently evaluated them. If there was a disagreement about which literature articles to choose, it was talked out with another reviewer (A.N.).

### ***Data extraction***

Two investigators (M.M. and M.P.) worked separately to choose studies that matched the aforementioned inclusion criteria. Data extraction disagreements were resolved by conversation with another reviewer (A.N.). A prepared form was used to collect the data. The data retrieved comprised publication characteristics (for example, first author name, year of publication, research design), population data (for example, number of participants, age, male sex), and IL-7 levels in designated groups (COVID-19 positive and negative patients; mild and moderate COVID-19 severity groups; severe and non-severe COVID-19).

### ***Quality and risk of bias assessment***

Five reviewers (M.M., A.B., A.H., M.P., and Y.S.) independently assessed the risk of bias in the individual studies. Inconsistencies were resolved through the consensus of all researchers involved in the data extraction process. We used the Newcastle-Ottawa scale (NOS) [25] to measure the methodological quality of observational studies based on their design. The NOS score was divided into three levels: low, moderate, and high quality. The NOS values were 0–5, 6–7, and 8–9. If there are

more than 10 studies in a single analysis, we do funnel plot analyses for asymmetry to explore probable publication bias.

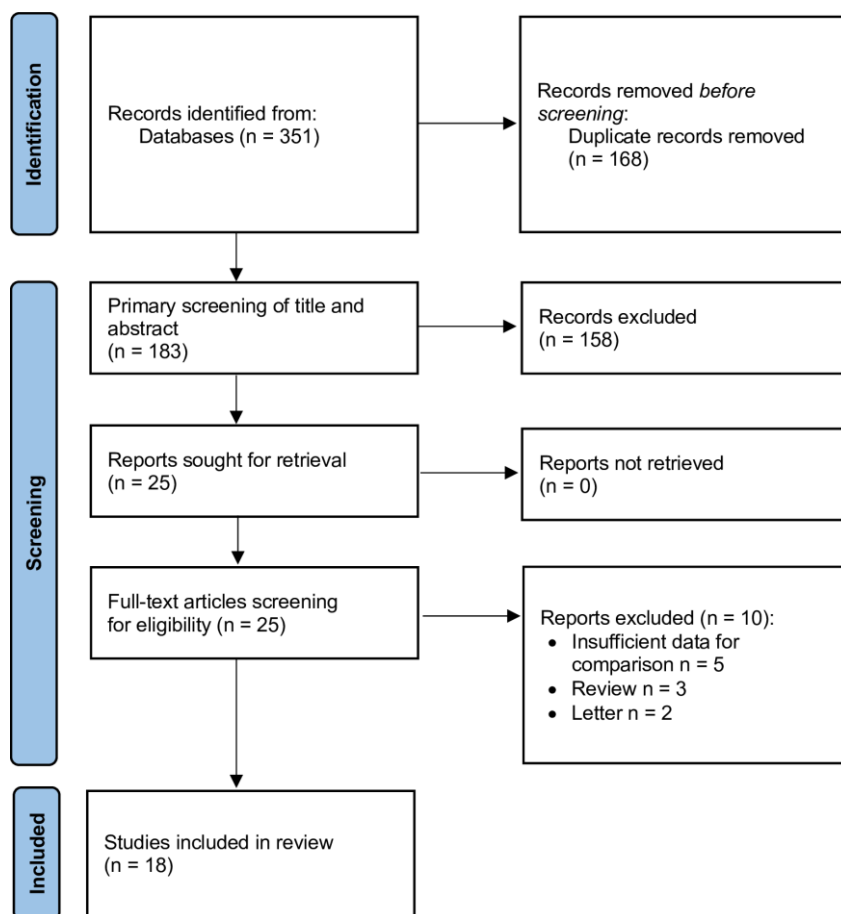
**Statistical analysis**

This meta-analysis was carried out according to the Cochrane Handbook. We use RevMan software (ver. 5.4, Cochrane Collaboration, UK) to analyze data. We utilized standardized mean differences (SMDs) as the impact metric with 95% confidence intervals to assess IL-7 levels (CIs). When IL-7 values were presented as medians with an interquartile range, Hozo's algorithm was used to calculate approximate means and standard deviations [26]. Heterogeneity was quantified using Cochran's Q statistics and Higgins' index ( $I^2$ ), with 25%, 50%, and 75% indicating moderate, substantial, and significant heterogeneity [24]. A random effects model was employed for all analyses; a fixed effects model was only used where specified in the results section for datasets with very low heterogeneity. To give quantitative proof, the Egger's test was performed. The significance level was set at P 0.05.

**RESULTS**

**Literature search**

The work flow of the process of study selection is demonstrated in Figure 2. A total of 351 articles were found in the initial database search. Of these, 183 studies remained after removing duplicate publications and screening through titles and abstracts. Among those, we identified 25 articles for full text review. Ultimately, all 18 studies with 2530 patients were included for review [27–44]. Table 1 shows the characteristics and risk of bias assessment of the included studies, respectively. Their overall quality was good. Studies originated in Italy, India, Turkey, Spain, Serbia, Switzerland, Mexico, Poland, Turkey, and the United States. Africa, Asia, Australia, Europe, North America, and South America. Table 1 shows the characteristics (such as sex, age, and BMI) of the patient populations of the studies included in the meta-analysis.



**Figure 2.** PRISMA study flow diagram.

**Table 1.** Baseline characteristics of included trials.

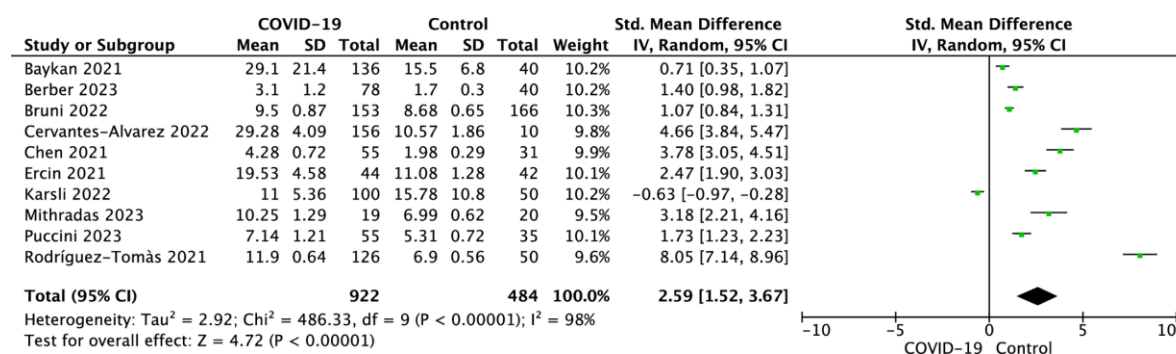
Study	Country	Study design	Study group	No. of participants	Age	Sex, male	BMI	NOS score
Baykan et al., 2021	Turkey	PS	COV-19 (+)	136	62.2 ± 14.7	67 (49.3)	NS	8
			COV-19 (-)	40	58.2 ± 9.3	16 (40.0)	NS	
Baykiz et al., 2022	Turkey	PS	Severe	48	63.08 ± 15.2	29 (60.4)	NS	8
			Non-severe	20	58.3 ± 11.9	16 (80.0)	NS	
			Survive	36	58.94 ± 13.4	22 (61.1)	NS	
			Decreased	32	64.75 ± 15.1	23 (71.9)	NS	
Berber et al., 2023	Turkey	PS	COV-19 (+)	78	58.8 ± 13.8	46 (59)	29.8 ± 5.8	9
			COV-19 (-)	40	55.0 ± 9.8	22 (55)	24.9 ± 2.9	
			Survive	58	57.3 ± 13.9	34 (58.6)	30.0 ± 6.2	
			Decreased	20	65.2 ± 10.3	12 (60.0)	29.0 ± 4.1	
Bruni et al., 2022	Switzerland	PS	COV-19 (+)	95	64 (52-75)	61 (64)	NS	8
			COV-19 (-)	75	71 (59-80)	42 (56)	NS	
Cervantes-Alvarez et al., 2022	Mexico	PS	COV-19 (+)	156	51.83 ± 12.73	107 (68.6)	29.39 (26.80-33.12)	9
			COV-19 (-)	10	NS	NS	NS	
			Severe	54	54.63 ± 11.52	42 (39.3)	29.35 (26.79-32.89)	
			Non-severe	102	50.97 ± 13.92	65 (60.7)	29.42 (26.80-33.40)	
Chen et al., 2021	Taiwan	RS	COV-19 (+)	55	46.8 ± 16.0	29 (52.7)	NS	8
			COV-19 (-)	31	40.2 ± 7.2	6 (19.4)	NS	
			Severe	24	NS	NS	NS	
			Non-severe	31	NS	NS	NS	
Erich et al., 2021	Turkey	PS	COV-19 (+)	44	54.6 ± 21.6	25 (56.8)	NS	8
			COV-19 (-)	42	39.3 ± 11.3	15 (35.7)	NS	
Gajovic et al., 2023	Serbia	RS	Severe	140	66.3±1.3	95 (67.9)	NS	8
			Non-severe	140	56.4±1.4	65 (46.4)	NS	
Karsli et al., 2022	Turkey	PS	COV-19 (+)	100	65.2 ±12.9	40 (40.0)	NS	8
			COV-19 (-)	50	65.32±16.1	19 (38.0)	NS	
			Severe	60	65.8±12.67	22 (36.7)	NS	
			Non-severe	40	64.05±13.5	18 (45.0)	NS	
Kazancioglu et al., 2021	Turkey	RS	Severe	29	NS	NS	NS	7
			Non-severe	55	NS	NS	NS	
			Control	56	NS	NS	NS	
Kusnierz-Cabala et al., 2021	Poland	PS	Severe	9	NS	NS	NS	7
			Non-severe	61	NS	NS	NS	
Mithradas et al., 2023	India	PS	COV-19 (+)	19	46.07 ± 7.19	NS	NS	7
			COV-19 (-)	20	39.47 ± 4.29	NS	NS	

Ozcan et al., 2022	Turkey	PS	Severe	64	56.9 ± 15.41	38 (59.37)	NS	8
			Non-severe	111	54.66 ± 15.34	60 (54.05)	NS	
Portacci et al., 2021	Italy	RS	Survive	101	63 (53.3-72)	30 (76.9)	NS	9
			Decreased	39	81 (71-86)	68 (67.3)	NS	
Puccini et al., 2023	Germany	RS	COV-19 (+)	55	69 (55-76)	38 (69.1)	26.7 (24.7-30.7)	9
			COV-19 (-)	35	73 (58-81)	20 (57.1)	25.1 (22.9-28.5)	
Rodríguez-Tomàs et al., 2021	Spain	RS	COV-19 (+)	126	71 (58-83)	30 (66.7)	NS	9
			COV-19 (-)	45	84 (75-89)	38 (76.0)	NS	
Tawiah et al., 2022	US	PS	Survive	308	57.8 ± 16.7	180 (58.4)	30.0±9.18	8
			Decreased	50	72.1 ± 14.8	30 (60.0)	28.2±7.94	
Turnic et al., 2022	Serbia	PS	Survive	32	46:50 ± 13:84	22 (68.7)	NS	7
			Decreased	15	72:53 ± 9:95	11 (73.3)	NS	

Note: BMI = body mass index; NOS = Newcastle Ottawa scale; NS = not specified; PS = prospective study; RS = retrospective study.

**Meta-analysis of included studies**

Ten studies provided data on the rate of Galectin-3 levels among patients with and without COVID-19. Pooled analysis showed that Galectin-3 levels among patients with and without COVID-19 varied and amounted to: 15.73±13.03 vs. 8.72±5.82 pg/mL, respectively (SMD = 2.59; 95%CI: 1.52 to 3.67; p<0.001; Figure 3).

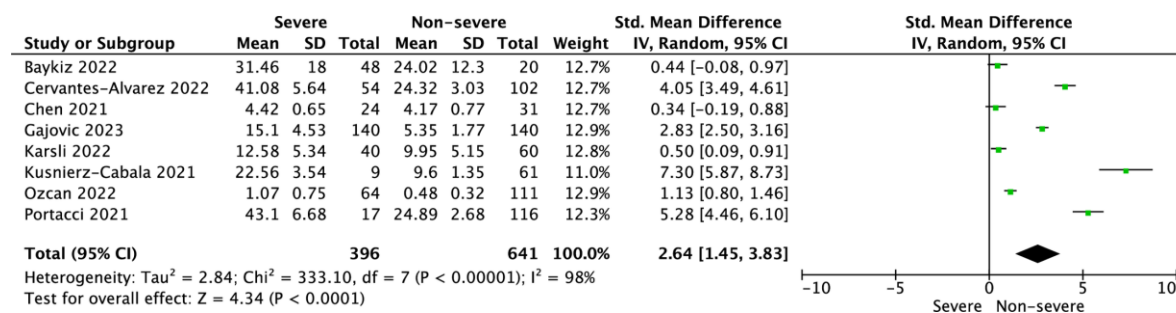


**Figure 3.** Forest plot of Galectin-3 levels among COVID-19 and control patients measured at baseline. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

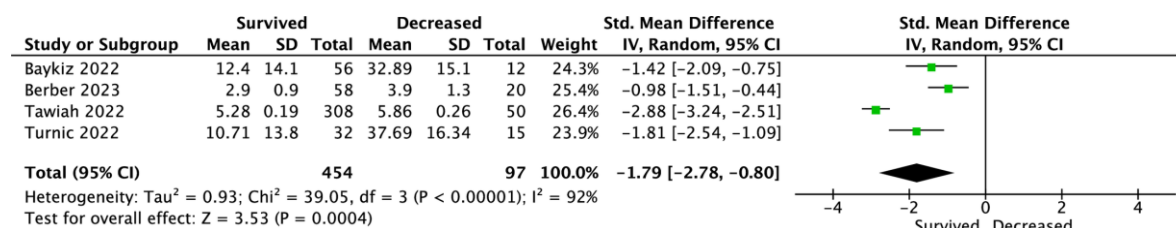
Pooled analysis of Galectin-3 levels among patients was 18.83±15.5 pg/mL in COVID-19 severe group, compared to 12.43±10.29 pg/mL in non-severe patients (SMD = 2.64; 95%CI: 1.45 to 3.83; p<0.001; Figure 4).

Four studies reported galectin-3 levels among COVID-19 patients who survive vs. deceased. Pooled analysis was 6.24±6.74 vs. 13.72±15.92 pg/mL (SMD = -1.79; 95%CI: -2.78 to -0.80; p<0.001; Figure 5). The results from the sensitivity analysis did not alter the direction.





**Figure 4.** Forest plot of Galectin-3 levels among severe vs. non-severe COVID-19 patients measured at baseline. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.



**Figure 5.** Forest plot of Galectin-3 levels among survived vs. decreased COVID-19 patients measured at baseline. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

## DISCUSSION

Our meta-analysis showed that the Galectin-3 concentration value among the severe group was statistically significantly higher compared to non-severe patients (18.83±15.5 pg/mL vs. 12.43±10.29 pg/mL, p<0.001). Of note, a statistically significant difference in Galectin-3 concentration also occurred among patients with and without COVID-19 (15.73±13.03 vs. 8.72±5.82 pg/mL, p<0.001, respectively). Although only four studies compared survived vs. died, statistical significance was obtained between the cohorts (6.24±6.74 vs. 13.72±15.92 pg/mL, p<0.001). To sum up, the results of our meta-analysis indicate that Galectin-3 may be a potential diagnostic and prognostic biomarker for patients with COVID-19 infection.

The results of our meta-analysis are partially consistent with the previously published meta-analysis from 2023. Behnoush et al. showed, similarly to ours, that patients with COVID-19 have statistically significantly higher Galectin-3 values compared to healthy controls. However, the above-mentioned meta-analysis did not show a statistically significant difference in the Galectin-3 value between severe and non-severe patients. What is worth noting is that the work by Behnoush et al. showed a tendency towards higher levels of Galectin-3 in severe COVID-19 patients compared to non-severe cases [45]. Moreover, contrary to our meta-analysis, Zhan et al. identified no statistically significant difference in Galectin-3 values between severe vs. mild/moderate cohorts [46]. A significant limitation in analyzing data regarding the severity of COVID-19 is the different approach to definitions. For example, Cervantes-Alvarez defined a severe outcome as the need for invasive mechanical ventilation as well as in-hospital death [31]. Moreover, the introduction of more subclasses within severity, e.g., mild, moderate, or severe, leads to even more prominent heterogeneity and interpretation difficulties. Mortality is usually defined as in-hospital mortality, which makes it easier to compare results. Still, the results from Berber et al. are similar to ours. They found that a cut-off of 2.8 ng/ml could predict death with an acceptable 80% sensitivity but an unacceptable 57% specificity [29].

Interestingly, galectin inhibitors, due to their blocking pro-inflammatory and pro-fibrotic properties, are a new class of drugs currently in the clinical trial phase that can be used in the treatment of COVID-19. The DEFINE clinical trial (phase Ib/IIa) confirmed that GB0139, a potent inhaled thiodigalactoside galectin-3, is well tolerated by patients, i.e., that the number of adverse reactions was similar between the group of patients receiving the GB0139 molecule and the so-called therapeutic standard (standard of care, SOC alone), 40 vs. 35, respectively. Among patients receiving GB0139, five adverse events were considered by investigators to be potentially related to the investigational medicinal product [47]. It is worth noting that the GB0139 molecule is undergoing extensive research (NCT02257177 and NCT03832946) in another therapeutic indication, idiopathic pulmonary fibrosis (IPF). However, further clinical trials involving a larger number of patients, including those with severe COVID-19, are needed to demonstrate whether the molecule can actually modify inflammation or fibrotic changes in the course of COVID-19 [48]. Moreover, an inhibitor of galectin-3 (Gal-3), in addition to its therapeutic properties, may prevent the transmission of COVID-19. ProLectin-M (PL-M), a Gal-3 antagonist, based on phase II results, proved to be safe, well-tolerated, and effective in reducing viral loads and rapid viral clearance [49].

The search for biomarkers that can predict the severity of COVID-19 remains an important theoretical and clinical problem. Fukui revealed that finding a biomarker that can be a good predictor of outcomes in the severe group is particularly difficult. Biomarkers such as C-reactive protein (CRP), presepsin (PSP), lactate dehydrogenase (LDH), and aspartate aminotransferase (AST) turned out to be good predictors of prognosis among less severe cases [50]. The economic issue is also important: the determination of biomarkers such as CRP or AST is much cheaper than in the case of more advanced biomarkers (e.g., Galectin-3). Biomarkers of inflammation, such as the previously mentioned CRP, are particularly useful in the prediction of outcomes among patients diagnosed with COVID-19 [51]. When looking for a useful predictive biomarker, the influence of ethnicity and gender should also be taken into account. Commonly used pro-inflammatory biomarkers, such as CRP, may be subject to bias; e.g., CRP values observed in men are usually higher at baseline [52]. Ethnicity also matters; one study found that among Asian and Caucasian patients, the CRP value among non-survivors was higher than among survivors. This correlation was not observed among black and Hispanic ethnicities [53]. Complex pro-inflammatory biomarkers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), or monocyte-lymphocyte ratio, may be less sensitive to issues of ethnicity and gender, although risks may also arise here. Unfortunately, Galectin-3 also appears to be susceptible to bias in this context. McEvoy et al. showed that Galectin-3 may be a useful biomarker for prognostication of death among patients with heart failure, but only among whites [54]. More attention is clearly needed to further evaluate the predictive properties of Galectin-3 in both ethnic and gender contexts.

Apart from the above-mentioned limitations regarding the variance in the definition of COVID-19 severity, some limitations will still be highlighted here. A standard limitation is the issue of cutoff, which allows stratification of patients with respect to outcomes. Another issue is the issue of standardizing the methods for determining Galectin-3. Moreover, the studies included in this meta-analysis were conducted over time, during which the therapeutic standard changed. The impact of this standard of care on the level of Galectin-3 cannot be determined; e.g., the use of strong treatment-modifying inflammatory activity could have influenced the value of Galectin-3. Some of the research may also have been conducted at the beginning of the pandemic, where staff shortages and a limited ability to introduce standardized research processes may have limited the usefulness of samples or influenced selection bias. Finally, the diagnostic properties of Galectin-3 are currently limited in practical applications due to the increasing number and types of diagnostic tests. Also, in the case of differential diagnosis, the value of Galectin-3 also increases in the course of other inflammatory and fibrotic diseases.

## **CONCLUSION**

The findings of our study highlight galectin-3 as a promising predictive biomarker for COVID-19 outcomes, revealing its potential in guiding clinical decisions. However, this conclusion warrants

further scrutiny. Future research should delve into the applicability of galectin-3 as a universally reliable biomarker, transcending ethnic and gender-based variations. It's crucial to investigate if galectin-3 maintains its predictive accuracy across diverse ethnic groups and genders, considering the variations in genetic makeup and physiological responses. This broader approach will ensure that the use of galectin-3 as a biomarker in COVID-19 can be effectively and equitably implemented in global healthcare, providing a more inclusive and accurate tool for managing the disease across different populations.

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