Original Article

A Systematic Review of Chest Computed Tomography and Biomarkers with an Emphasis on Sensitivity and Specificity to Assess Diagnostic Accuracy and Prognostic Value in COVID-19

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Abstract

Objective: This systematic review seeks to assess the diagnostic accuracy of Chest Computed Tomography (CT) in detecting COVID-19 and evaluate the prognostic significance of key biomarkers, emphasizing sensitivity and specificity.

Material and Methods: A thorough literature search was conducted in PubMed, Scopus, and Web of Science for original research articles published from January 2020 to October 2022. Inclusion criteria comprised studies reporting on the diagnostic accuracy of Chest CT and the prognostic value of biomarkers in COVID-19 patients. Data extraction included study characteristics, participant demographics, and relevant diagnostic and prognostic metrics. Quality assessment tool, Newcastle-Ottawa Scale and QUADAS-2 tool were utilized to evaluate the risk of bias.

Results: Forty-four studies with 19,327 participants were included in this systematic review. The diagnostic sensitivity of chest computed tomography (CT) ranges from 0.73 to 0.99, indicating a generally high capacity of Chest CT to identify COVID-19 cases. However, specificity varies from 0.25 to 0.90, suggesting challenges in distinguishing COVID-19 from other respiratory conditions solely based on CT findings. D-Dimer emerges as a prominent biomarker with varying sensitivity (0.52 to 0.92) and specificity (0.22 to 0.75).

Conclusion: Systematic review emphasizes the need for contextual interpretation of CT chest to diagnose COVID-19. The blood biomarkers can be helpful in predicting disease severity, but cutoffs and significance need to be validated.

Keywords: COVID-19, SARS-CoV-2, Coronavirus, Novel Coronavirus, Diagnostic Accuracy.

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Introduction

The global efforts to combat the COVID-19 pandemic prompted a continuous exploration of effective diagnostic and prognostic tools to enhance our understanding and management of the disease.[1] Among the various investigative approaches, Chest Computed Tomography (HRCT) emerged as a focus of research.[2] Several studies have investigated the potential of Chest CT scan as a diagnostic tool for COVID-19, particularly highlighting its sensitivity considering this imaging modality as a valuable primary screening tool, especially in regions heavily affected by the epidemic.[3] On the other hand, its role in detecting COVID-19 has been underscored at other places.[4] Despite the observed high sensitivity, concerns have been raised about the specificity of Chest CT, prompting questions about its widespread applicability in diverse epidemiological contexts.[5] Simultaneously, there has been a collective effort to

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identify reliable prognostic biomarkers capable of predicting disease severity in the early stages of COVID-19.6 Biomarkers such as D-Dimer, Lactate Dehydrogenase (LDH), Neutrophil count, Lymphocyte count, and Interleukin-6 (IL-6) among others have emerged as promising indicators for assessing disease progression and predicting adverse outcomes.[7,8]

This systematic review aims to present a comprehensive and critical analysis of the existing literature regarding the diagnostic accuracy of Chest CT in detecting COVID-19. Additionally, we explore the performance of key biomarkers in predicting disease severity, providing a nuanced understanding of their role in clinical decision-making. By synthesizing evidence from diverse studies, our goal is to contribute valuable insights into the utility and limitations of these diagnostic and prognostic tools. Such insights are crucial for guiding healthcare practitioners in decision-making processes and informing future research efforts to refine strategies in the aftermath of the pandemic.

Material and Methods

1. Formulation of Research Questions:

The systematic review aims to address two primary research questions:

- What is the diagnostic accuracy of Chest Computed Tomography (CT) in detecting COVID-19?
- What is the prognostic value of key biomarkers in predicting disease severity in COVID-19 patients?

In the context of a systematic review focusing on the diagnostic accuracy of Chest Computed Tomography (CT) in detecting COVID-19 and the prognostic significance of biomarkers, the PICO framework can be outlined as follows:

Population (P): Individuals with suspected or confirmed COVID-19.

Intervention (I): Diagnostic accuracy of Chest Computed Tomography (CT) for detecting COVID-19. Prognostic value of biomarkers (e.g., D-Dimer, Lactate Dehydrogenase, Neutrophil-to-Lymphocyte Ratio, Interleukin-6, C-reactive protein) in predicting disease severity in COVID-19 patients.

Comparison (C): For diagnostic accuracy: Comparison with reference standards such as RT-PCR. For prognostic biomarkers: Comparison of different biomarkers and their predictive value.

Outcome (O): Diagnostic accuracy outcomes, including sensitivity, specificity, positive predictive value, and negative predictive value of Chest CT. Prognostic outcomes, including the association between biomarker levels and disease severity or clinical outcomes in COVID-19 patients.

2. Search Strategy:

In this systematic review, an exhaustive exploration of the literature was carried out across electronic databases, including PubMed, Scopus, and Web of Science, to compile pertinent studies on the diagnostic accuracy of Chest Computed Tomography (CT) in detecting COVID-19 and the prognostic implications of specific biomarkers. The search strategy employed a blend of Medical Subject Headings (MeSH) terms and keywords, encompassing:

- COVID-19

  - Keywords: COVID-19, SARS-CoV-2, coronavirus, novel coronavirus
- Chest Computed Tomography (CT)

  - Keywords: chest CT, computed tomography, HRCT chest, radiographic imaging, imaging accuracy
- Diagnostic Accuracy

  - Keywords: diagnostic accuracy, sensitivity, specificity, diagnostic criteria
- Prognostic Biomarkers

  - Keywords: prognostic, predictive, biomarkers, D-Dimer, Lactate Dehydrogenase (LDH), Neutrophil-to-Lymphocyte Ratio (NLR), Neutrophil count, Lymphocyte count, Total leucocyte count (TLC) Differential Leucocyte count (DC), Interleukin-6 (IL-6), C-reactive protein (CRP).

The formulation of search queries involved the use of Boolean operators (AND, OR) to refine and enhance search precision. For example:

- (COVID-19 OR SARS-CoV-2) AND ("Tomography, X-Ray Computed" OR chest CT) AND ("Sensitivity and Specificity" OR diagnostic accuracy) AND (D-Dimer OR LDH OR NLR OR IL-6 OR CRP OR TLC OR DLC OR Creatinine OR Cardiac Troponin).

This approach ensured a thorough exploration of the literature, encompassing diverse aspects of diagnostic accuracy and prognostic biomarkers associated with COVID-19 and Chest CT."

3. Inclusion and Exclusion Criteria:

Studies were included based on the following criteria:

- Original research articles published in peer-reviewed journals.
- Studies reporting diagnostic accuracy of Chest CT for COVID-19 detection or the prognostic value of specific biomarkers in predicting disease severity.
- Studies published between January 2020 and the present to capture the evolving understanding of COVID-19.

Exclusion criteria:

- Non-English language publications.
- Review articles, case reports, and editorials.
- Studies with insufficient data on diagnostic accuracy or prognostic value.
- Preprints and studies without peer review, unpublished data

4. Study Selection:

Two independent reviewers (AA and MR) conducted the initial screening of titles and abstracts based on the inclusion and exclusion criteria. Full-text articles of potentially relevant studies were then assessed for eligibility We included studies of all designs that produce estimates of test accuracy or provide data from which estimates can be computed: cross-sectional studies, case-control designs and consecutive series of patients assessing the diagnostic accuracy of HRCT chest and routine laboratory testing as prognostic tests to determine disease severity of COVID-19. Discrepancies were resolved through consensus, and a third reviewer was consulted if needed.

5. Data Extraction:

Data were systematically extracted from selected studies using a standardized form. The following information was collected:

- Study characteristics: author, publication year, study design.
- Participant characteristics: sample size, demographics, clinical setting.
- Diagnostic accuracy of Chest CT: sensitivity, specificity, positive predictive value, negative predictive value, accuracy.
- Prognostic biomarkers: types, sensitivity, specificity, predictive values.

6. Quality Assessment:

The quality of included studies was assessed using relevant tools such as the QUADAS-2 tool for diagnostic accuracy studies and the Newcastle-Ottawa Scale for prognostic studies. This step aimed to evaluate the risk of bias and methodological quality of each study.

7. Data Synthesis and Analysis:

A narrative synthesis approach was employed to summarize findings from included studies. Diagnostic accuracy results were presented in tabular form, detailing sensitivity, specificity, and other relevant metrics. Prognostic biomarker data were synthesized to provide an overview of their association with disease severity.

8. Ethical Considerations:

As this systematic review involved the analysis of published data, ethical approval was not required. The review adhered to ethical guidelines, and data were handled in accordance with principles of confidentiality and privacy.

9. Reporting:

The systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and completeness in reporting.

10. Limitations:

Potential limitations of the review include the heterogeneity of study designs, populations, and methodologies across included studies. The evolving nature of the COVID-19 pandemic may also impact the generalizability of findings.

Results and Discussion

The sensitivity and specificity are frequently used to assess the diagnostic performance of a biomarker. Sensitivity is the capacity to identify a disease in patients where the disease is present (i.e., a true positive). In contrast, specificity is the capacity to rule out the disease in patients where the illness is truly absent. Because a biomarker might offer a diagnosis or estimate severity, the findings and discussion for sensitivity and specificities of HRCT and blood assays are tabulated and analyzed below.

Characteristics of Included Studies

Table 1: *Characteristics of included studies*

	Author	Study Design	Country	Cohort Size	Biomarkers studied / HRCT scan (if done)	Comments	NOS score
1.	Wang et al. 2020 [9]	Retrospective Cohort, single center	China	138	Neutrophil count, Lymphocyte count, LDH	Higher Neutrophil count, LDH and lower lymphocyte count are significantly correlated to severe critical cases	9
2.	Yang et al. 2020 [10]	Retrospective Cohort, multi center	China	149	Neutrophil count, Lymphocyte count, D-dimer, albumin, AST, creatinine, LDH, CRP, HRCT	CT scan cannot exclude the diagnosis of COVID-19 as some patients with COVID-19 can present with normal chest finding however high biomarkers levels can have diagnostic and prognostic prediction	6
3.	Zhou et al. 2020 [11]	Retrospective Cohort	China	191	Lymphocyte count, albumin, D-dimer, IL-6, creatinine,	Considered D-dimer > 4 g/mL could help clinicians to identify patients with poor prognosis at an early stage	7
4.	Diao et al. 2020 [12]	Retrospective Cohort	China	522	Lymphocyte count, IL-6	Reduction in T cell counts (<200 cells/cubic mm) and functionally exhausted T cells have poor prognosis in COVID-19 patients.	6
5.	Liu et al. 2020 [13]	Retrospective cohort, single center	China	40	Neutrophil count, Lymphocyte count, AST, LDH, creatinine, D-dimer, CRP	Higher degree of lymphopenia and proinflammatory cytokines are associated with COVID-19 disease severity.	8
6.	Feng et al. 2020 [14]	Retrospective cohort, single center	China	132	Lymphocyte count, Neutrophil count, CRP, IL-6, HRCT	Proposed CT scan as early screening could not satisfy every patient in COVID-19 outbreak and considered use of machine-learning algorithms to analyze clinical symptoms, biomarkers, and other clinical information as a good tool for diagnosis and early prediction of cases prognosis before further CT examination	7
7.	Qin et al. 2020 [15]	Retrospective cohort, single center	China	452	CRP, IL-6, Neutrophil count, Lymphocyte count	Compared inflammatory biomarkers levels in severe and non-severe COVID-19 cases	8
8.	Liu et al. 2020 [16]	Retrospective cohort, single center	China	140	IL-6, lymphocytes, neutrophils, AST, CRP, Creatinine, D-Dimer	Measured different biomarkers and correlated them with disease progression	6
9.	Wu et al. 2020 [17]	Retrospective cohort, single center	China	201	IL-6	Significantly correlated higher IL-6 (> 45 pg/ml) levels with disease severity	6
10.	Chen et al. 2020 [18]	Retrospective cohort, single center	China	99	IL-6	Considered high IL-6 levels one of the measures that may detect COVID-19 severity.	8
11.	Ji et al. 2020 [19]	Retrospective cohort, single center	China	33	CRP	Gives cutoff levels of CRP in COVID 19 patients with severe disease	7
12.	Etoga et al. 2020 [20]	Cross sectional single center	Came-roon	80	Cortisol	Observed higher levels of cortisol among COVID-19 cases who need further oxygen therapy as compared to cases with mild disease	9
13.	Ramezani et al. 2020 [21]	Cross sectional single center	Iran	30	Cortisol	This study significantly correlated higher levels of cortisol in non-survived patients of	6

14.	Li et al. 2020 [22]	Retrospective cohort, single center	China	132	CRP	This study recorded significant difference of CRP between mild and severe critical cases	7
15.	Tang et al. 2020 [23]	Retrospective cohort single center	China	183	D-Dimer	Recorded higher levels of D-Dimer among 16 non- survivor COVID-19 cases	6
16.	Zhang et al. 2020 [24]	Retrospective cohort single center	China	343	D-Dimer	They study considered D-dimer level on admission > 2.0 g/mL could effectively predict hospital mortality in patients with COVID-19	8
17.	Huang et al. 2020 [25]	Prospective cohort single center	China	41	IL-6, D-Dimer	Recorded higher levels of IL-6 and D-dimer among severe cases	7
18.	Cheng et al. 2020 [26]	Prospective cohort single center	China	701	Creatinine	They correlated high level of creatinine with severity and worse outcome in COVID-19 cases	8
19.	Luo et al. 2020 [27]	Retrospective cohort single center	China	35	LDH	Considered higher levels of LDH may indicate severity of the disease by their recorded levels of LDH in severe cases	6
20.	Li et al. 2020 [28]	Retrospective cohort single center	China	134	Lymphocyte count, Neutrophils count, D-Dimer, albumin, AST, Creatinine, IL-6, CRP	Reached cut off value for decrease in albumin levels with the progression of the disease even they considered it as an independent predictor (cut-off point: 35.1 g/L) of the risk of non survivors among critical COVID-19 cases	6
21.	Ferrari et al. 2020 [29]	Retrospective cohort single center	Italy	207	LDH	LDH higher level among COVID-19 cases and considered it may help in diagnosis of such cases	8
22.	Mo et al. 2020 [30]	Retrospective cohort single center	China	155	LDH	Recorded higher levels among complicated cases and correlated LDH biomarker with the development of the disease.	7
23.	Tao Ai, et al. 2020 [31]	Retrospective study	China	101	Chest CT	Chest CT has a high sensitivity for diagnosis of coronavirus disease 2019 (COVID-19). Chest CT may be considered as a primary tool for the current COVID-19 detection in epidemic areas.	6
24.	Kristof De Smet, et al. 2021 [32]	Retrospective secondary analysis	North America	197	Chest CT for SARS-CoV-2 Infection	Sensitivity in asymptomatic individuals was insufficient to justify its use as a first-line screening approach.	8
25.	Karimian, M. et al. 2020 [33]	Retrospective study	China	40 eligible studies with 4,183 patients	HRCT, Chest computed tomography	This study showed that HRCT in diagnosis of COVID-19.	7
26.	Lv, M. et al. 2020 [34]	Retrospective study	China	103 studies with 5,673 patients	Chest computed tomography	The sensitivity of chest HRCT in COVID-19 is 99%, suggesting that CT has the potential to be used as an assisting diagnostic tool.	9
27.	Huang, E. et al. 2020 [35]	Retrospective study	China	372	Computed tomography, RT-PCR	Results show high sensitivity, but poor specificity limits the routine use of chest CT as a primary tool for COVID-19 detection.	8

28.	Kim, H. et al. 2020 [36]	Retrospective study	China	217	CT and Reverse Transcriptase-Polymerase	The chest CT scans for the primary screening or diagnosis of coronavirus disease 2019 would not be beneficial in a low-prevalence region due to the substantial rate of false-positives. A cost-effectiveness analysis and assessment of practicability are warranted for chest CT in high-prevalence regions.	7
29.	Chang, T. et al. 2020 [37]	Retrospective study	Taiwan	189	Chest CT, Clinical characteristics and diagnostic challenges of pediatric COVID-19	The diagnosis is based mainly on typical ground glass opacities on chest CT and dominant is diagnosis of COVID-19.	6
30.	Hanif, et al. 2021 [38]	Descriptive study	Pakistan	94	HRCT Chest and RT-PCR	HRCT is not only superior in diagnosing COVID-19, but it is also prompt and commonly available. Thus, it is suggested that it may be implied as first line diagnostic test at least in time of pandemic.	7
31.	Guan et al. (2020) [39]	Cohort Study	China	109	D-Dimer	D-dimer levels much higher in those requiring ICU admission and invasive ventilation however statistical analysis not performed.	7
32.	Shi et al. (2020) [40]	Cohort Study	China	416	Cardiac Troponin	Significantly higher levels of hs-TnI in patients who require mechanical ventilation compared to those who do not	6
33.	Zhan et al. 2021 [41]	Cohort study	China	640	D-Dimer	D-dimer can predict severe and fatal cases of COVID-19 with moderate accuracy	8
34.	Ali et al. 2021 [42]	Cross-sectional study	Pakistan	70	HRCT Chest, PCR	High-resolution computed tomography (HRCT) is a reliable diagnostic approach in promptly detecting the COVID-19	7
35.	Abdelhady et al. 2022 [43]	Cross sectional study	Egypt	155	D-dimer, CRP, LDH, NLR and serum ferritin were assessed.	NLR with ferritin and LDH markers had higher degree of sensitivity and specificity in detecting adverse outcomes in COVID-19 patients.	7
36.	Butt et al. 2022 [44]	Retrospective cohort study	Pakistan	199	CORADS, CTSS, HRCT, RT-PCR	HRCT chest has high sensitivity and negative predictive value for diagnosis of COVID pneumonia on the basis of CORADS reporting scheme. However it has low specificity	6
37.	Milenkovic et al. 2022 [45]	Retrospective cohort	Serbia	318	D-Dimer, CRP, IL-6, PCT	IL-6 ≥ 74:98 pg/mL, CRP values ≥ 81 mg/L, procalcitonin ≥ 0:56 ng/mL, and D-dimer ≥ 760 ng/mL could effectively predict in-hospital mortality in COVID-19 patients.	6
38.	Gempeler et al. 2022 [46]	diagnostic test accuracy retrospective study	Colombia, UK, US	110	HRCT Chest, PCR, trauma	HRCT appears to be an additional screening tool that can easily detect PCR false negatives, which are reportedly highly frequent.	8
39.	Shim et al, 2022 [47]	Retrospective cohort study	Korea	210	HRCT, RDT, US as compared to RT-PCR	No significant difference between HRCT, RDT, US as compared to RT-PCR.	9
40.	Ebrahimzadeh et al, 2022 [48]	Retrospective	UK	51	Chest CT, SARS-CoV-2 infection	Chest CT is sensitive and moderately specific in diagnosing COVID-19. Thus, chest CT may have more utility for ruling out COVID-19 than for differentiating SARS-CoV-2	7

41.	Trujillo-Rodriguez et al. 2022 [49]	Prospective, multicenter	Spain	333	CRP, D-Dimer, LDH, IL-6, IL-8, IL-1β, TNF-α, (IFN-γ), macrophage inflammatory proteins 1α (MIP-1α) and β (MIP-1β), Interferon gamma-induced protein 10 (IP-10) and sCD25	LDH, D-dimers, neutrophil-lymphocyte ratio (NLR), and oral corticosteroids treatment were predictors of early discharge.	7
42.	Kashyapee et al, 2021[50]	Retrospective, cross-sectional study	India	1499	HRCT	HRCT is an excellent adjunct for initial diagnosis of COVID-19 pneumonia in both symptomatic and asymptomatic individuals in addition to the role of prognostic indicator for COVID-19 pneumonia.	6
43.	Pizzi et al, 2021 [51]	Retrospective study	Italy	120	HRCT	HRCT proved helpful in differentiating ground glass opacities of Covid-19 from Non-Covid-19 cases.	8
44.	Cho et al, 2021 [52]	Single-center retrospective cohort study	United States	158	D-Dimer	D-dimer levels are uniformly elevated in patients with COVID-19. Although standard predictive criteria failed to predict DVT, this analysis showed a D-dimer of less than 6494 ng/mL may exclude DVT.	6

Table 2: *Diagnostic accuracy of Chest Computed Tomography (CT) in detecting COVID-19*

	Author	**Test Performance (Overall)**			**Comments**
		Sensitivity (%)	**Specificity (%)**	**Accuracy**	
1.	Tao Ai, et al. 2020 [31]	0.97	0.25	Yes	Chest CT has a high sensitivity for diagnosis of coronavirus disease 2019 (COVID-19). Chest CT may be considered as a primary tool for the current COVID-19 detection in epidemic areas.
2.	Kristof De Smet, et al. 2021 [32]	0.89	0.73	Yes	Sensitivity in asymptomatic individuals was insufficient to justify its use as a first-line screening approach.
3.	Karimian, M. et al. 2020 [33]	0.95	---	Yes	This study showed that HRCT scan has little weakness in diagnosis of COVID-19.
4.	Lv, M. et al. 2020 [34]	0.99	---	Yes	The sensitivity of chest HRCT in COVID-19 is 99%, suggesting that CT has the potential to be used as an assisting diagnostic tool.
5.	Huang, E. et al. 2020 [35]	0.95	0.64	Yes	Results show high sensitivity, but poor specificity limits the routine use of chest CT as a primary tool for COVID-19 detection. Chest CT should only be arranged for individuals with certain clinical features in conjunction with RT-PCR tests.
6.	Kim, H. et al. 2020 [36]	0.94	0.37	Yes	The chest CT scans for the primary screening or diagnosis of COVID 19 would not be beneficial in a low-prevalence region due to the substantial rate of false-positives. A cost-effectiveness analysis and assessment of practicability are warranted for chest CT in high-prevalence regions.
7.	Chang, T. et al. 2020 [37]	0.93	---	Yes	The diagnosis is based mainly on typical ground glass opacities on chest CT and dominant is diagnosis of COVID-19.

8.	Hanif, et al. 2021[38]	0.92	0.23	Yes	HRCT is not only superior in diagnosing COVID-19, but it is also prompt and commonly available. Thus, it is suggested that it may be implied as first line diagnostic test at least in time of pandemic.
9.	Ali et al. 2021[42]	0.91	0.90	YES	High-resolution computed tomography (HRCT) is a reliable diagnostic approach in promptly detecting the COVID-19
10.	Butt et al. 2022 [44]	0.99	0.37	Yes	HRCT chest has high sensitivity and negative predictive value for diagnosis of COVID pneumonia on the basis of CORADS reporting scheme. However, it has low specificity
11.	Gempeler et al. 2022 [46]	0.91	0.73	YES	HRCT appears to be an additional screening tool that can easily detect PCR false negatives, which are reportedly highly frequent.
12.	Shim et al, 2022 [47]	0.85	0.879	Yes	No significant difference between HRCT, RDT, US as compared to RT-PCR.
13.	Ebrahimzadeh et al, 2022 [48]	0.91	0.56	Yes	Chest CT is sensitive and moderately specific in diagnosing COVID-19. Thus, chest CT may have more utility for ruling out COVID-19 than for differentiating SARS-CoV-2 infection from other causes of respiratory illness.
14.	Kashyapee et al, 2021 [50]	0.73 (Asymptomatic) 0.71 (symptomatic	0.50 (Asymptomatic) 0.57 (symptomatic)	Yes	HRCT is an excellent adjunct for initial diagnosis of COVID-19 pneumonia in both symptomatic and asymptomatic individuals in addition to the role of prognostic indicator for COVID-19 pneumonia.
15.	Pizzi et al, 2021 [51]	0.93	0.75	Yes	HRCT proved helpful in differentiating ground glass opacities of Covid-19 from Non-Covid-19 cases.

Table 3: *Prognostic value of biomarkers in predicting disease severity in COVID-19 patients*

Authors	Biomarkers	Sensitivity	Specificity	Comments
Tang et al. (2020) [23]	**D-Dimer**	0.77	0.61	Abnormal coagulation results with markedly elevated D -dimer (>12 µg/mL) are common in deaths with COVID-19
Zhou et al. (2020) [11]		0.52	0.6	D-dimer levels > 6 µ g/mL can help clinicians in identifying patients with poor prognosis at earlier stage
Guan et al. (2020) [39]		0.63 with	0.43 with	D-dimer levels much higher (>05 mg/L) in those requiring ICU admission and invasive ventilation however statistical analysis not performed.
Zhang et al. (2020) [24]		0.73	0.69	D-dimer on admission of >4.0 µg/mL could effectively predict in-hospital mortality in patients with COVID -19 and could be an early and helpful marker to improve management
Abdelhady et al. 2022 [43]		0.92	0.22	Role of D-Dimer is predictive in outcome of Covid-19.
Zhan et al. (2021) [41]		0.77	0.71	D-dimer can predict severe and fatal cases of COVID -19 with moderate accuracy. It also shows high sensitivity but relatively low specificity for detecting COVID-19 - related VTE events, indicating that it can be used to screen for patients with VT
Milenkovic et al. 2022 [45]		0.64	0.57	cutoff value of D -Dimer was 760 ng/ Ml. T his can effectively predict in hospital mortality in Covid-19 patients.
Trujillo-Rodriguez et al. 2022 [49]		0.69	0.75	D-dimers <698 ng/mL is associated with discharge during first week.

Cho et al, 2021 [52]		0.81	0.69	optimal D-dimer cutoff of 6494 ng/mL is helpful in determining the presence of deep vein thrombosis (DVT) in coronavirus disease-19 (COVID-19)-positive patients.
Abdelhady et al. 2022 [43]	**LDH**	0.79	0.47	NLR with ferritin and LDH markers had higher degree of sensitivity and specificity in detecting adverse outcomes in COVID-19 patients.
Luo et al. 2020 [27]		0.73	---	Higher LDH levels reported in severe patients.
Guan et al. 2020 [39]		0.58	0.47	Higher LDH >350 U/L levels present in majority of severe patients
Mo P et al. 2020 [30]		0.63	0.37	Higher LDH levels >625U/L present in majority of severe patients
Wang et al. 2020 [9]		0.43	0.21	Higher LDH > 400 U/L levels present in majority of severe patients
Trujillo-Rodriguez et al. 2022 [49]		0.69	0. 74	LDH <337 UI/L is associated with early discharge during first week.
Abdelhady et al. 2022 [43]	**Neutrophils/ NLR**	0.92	0.21	NLR can predict the adverse outcome (e.g., disease deterioration and shock) at cut-off 6.65, with 92% sensitivity and 20.7% specificity
Qin et al. 2020 [15]		0.67	0.32	Significantly higher in severe patients. Monitoring may aid in early screening of critical illness.
Wang et al. 2020 [9]		0.79	0.27	Severe patients had drastically lower WCC, checking low LC and high NC may help in early detection of disease progression.
Chen N et al. 2020 [18]		----	0.53	Surveillance of NC may reflect severity of lung abnormalities.
Trujillo-Rodriguez et al. 2022 [49]		0.69	0.74	NLR <4.76 is associated with discharge during first week.
Qin et al. 2020 [15]	**Lymphocyte s**	0.88	----	Significantly higher in severe patients. Monitoring may aid in early screening of critical illness.
Wang et al. 2020 [9]		0.8	0.60	Severe patients had drastically lower WCC, checking low LC and high NC may help in early detection of disease progression.
Chen N et al. 2020 [18]		----	0.9	Surveillance of LC may reflect severity of lung abnormalities.
Qin et al. 2020 [15]	**Total leucocyte count (TLC)**	0.56	0.49	Significantly higher > 22000/microliter in severe patients. Monitoring may aid in early screening of critical illness
Wang et al. 2020 [9]		0.66	0.43	Severe patients had drastically lower WCC, checking low LC and high NC may help in early detection of disease progression.
Chen N et al. 2020 [18]		----	0.73	Surveillance of WCC may reflect severity of lung abnormalities.
Chen et al. 2020 [18]	**Interleukin-6**	0.61	0.34	Increased expression of IL-6 (72 ± 12 in serum is expected to predict the severity of COVID-19
Liu et al. (2020) [13]		0.36	0.24	Severity of COVID-19 could be predicted with baseline IL-6 levels
Diao et al (2020) [12]		0.86	----	Significantly higher baseline levels of IL-6 (167 mg/dl) in those requiring ICU compared to those who do not
Huang et al (2020) [25]		0.61	0.53	Significantly higher baseline levels of IL-6 in those requiring ICU compared to those who do not
Qin et al (2020) [15]		0.25	0.13	Significantly higher levels of IL-6 in severe and critical COVID-19. Surveillance may help in early screening of critical illness

Milenkovic et al. 2022 [45]		0.70	0.63	cutoff value of IL-6 for in-hospital death prediction was 74.98 pg/mL.
Abdelhady et al. 2022 [43]	**C-reactive protein**	0.89	0.21	Role of CRP (66.04 ± 44.89)is predictive in outcome of Covid-19.
Li H, et al. 2020 [22]		0.76	0. 56	Critically severe patients had significantly higher CRP than severe patients. (83.22 ± 32.21)
Liu et al. 2020 [13]		0.94	0.56	Significantly more patients in the severe group experienced higher CRP levels vs non-severe.
Qin et al. 2020 [15]		0.58	0.33	Higher levels of CRP (103.2—204 mg/dl) recorded in the severe group vs non-severe group are suggestive that CRP can be monitored to assess progression of disease.
Ji et al. 2020[19]		0.56	0.23	Stratifies patients by direct and indirect contact to Wuhan – does not assess severity
Wang et al. 2020 [9]		0.53	---	Greater CRP (>54.15) values are more prominent in critical group – indicating lung damage.
Milenkovic et al. 2022 [45]		0.67	0.60	cutoff value of CRP was 81 mg/L predictive of in hospital mortality.
Zhou et al. (2020) [11]	**Cardiac Troponin**	0.56	0.03	Significantly higher levels of hs-TnI in non-survivors compared to survivors
Shi et al. (2020) [40]		0.61	----	Significantly higher levels of hs-TnI in patients who require mechanical ventilation compared to those who do not
Cheng et al. 2020 [18]	**Creatinine**	0.39	0.77	Raised creatinine levels (> 4.5 md/dl) associated with poor outcome in COVID-19 infection.
Zhou et al. 2020 [11]		0.71	0.65	Serum creatinine on admission can effectively highlight kidney impairment in COVID 19 patients.

Diagnostic Accuracy of Chest CT in Detecting COVID-19

The diagnostic accuracy of Chest Computed Tomography (CT) in detecting COVID-19 is a subject of considerable interest, with varied findings across studies.

Several studies highlight the utility of Chest CT as a primary tool for COVID-19 detection, especially in epidemic areas where the prevalence is high.[8,34] However, concerns arise regarding the specificity of Chest CT, limiting its routine use as a standalone diagnostic tool.[35] In regions with lower prevalence, the substantial false-positive rate may impede the cost-effectiveness of Chest CT as a primary screening approach.[36]

The findings suggest a nuanced approach, advocating for the judicious use of Chest CT in conjunction with other diagnostic methods, such as RT-PCR tests, particularly for individuals with specific clinical features. This aligns with the recommendations of various studies.[35,36]

Prognostic Value of Biomarkers in Predicting Disease Severity

Table 3 presents the prognostic value of key biomarkers in predicting disease severity in COVID-19 patients. Notably, D-Dimer emerges as a prominent biomarker with varying sensitivity (0.52 to 0.92) and specificity (0.22 to 0.75). Elevated D-Dimer levels are consistently associated with adverse outcomes, including mortality, suggesting its role as a crucial prognostic indicator.[23,43]

Lactate Dehydrogenase (LDH) and Neutrophil-to-Lymphocyte Ratio (NLR) also exhibit prognostic significance, with varying sensitivity and specificity values. Higher LDH levels are consistently observed in severe cases, aligning with previous studies highlighting its association with adverse outcomes.[27,30]

NLR, a composite marker, stands out with a high sensitivity of 0.92, indicating its potential to predict adverse outcomes. The combination of NLR with other markers like ferritin and LDH enhances sensitivity and specificity, reinforcing its utility in assessing disease progression.[43]

Inflammatory markers such as Interleukin-6 (IL-6) and C-reactive protein (CRP) also show promise in predicting disease severity. IL-6 exhibits varying sensitivity (0.25 to 0.86) and specificity (0.13 to 0.75), emphasizing its potential as an early indicator of severe cases.[13,25] CRP, with a sensitivity range of 0.53 to 0.94, demonstrates its role in predicting adverse outcomes, aligning with studies associating higher CRP levels with disease severity.[22,19]

Future Directions and Limitations

Navigating the complex terrain of COVID-19 diagnostics and prognostics underscores the need for future research to refine the integration of Chest CT with other diagnostic modalities. Addressing concerns about specificity, especially in regions with varying prevalence rates, necessitates tailored approaches to optimize the cost-effectiveness of Chest CT in COVID-19 detection.

In the realm of biomarkers, there is a compelling need for longitudinal studies that track the dynamics of these markers over the course of the disease. Understanding how biomarkers evolve could provide crucial insights into their utility in predicting disease progression and guiding timely interventions.

Despite the valuable contributions of existing studies, it is imperative to acknowledge the limitations inherent in the current body of evidence. The heterogeneity of study designs, patient populations, and methodologies across the included studies introduces potential sources of bias and may impact the generalizability of findings. Future research endeavors should strive for standardized methodologies, larger and more diverse cohorts, and collaboration across institutions to generate more robust and widely applicable conclusions.

Conclusion

In conclusion, this extended discussion seeks to unravel the complexities surrounding the diagnostic accuracy of Chest CT and the prognostic value of biomarkers in the context of COVID-19. The multifaceted nature of these diagnostic and prognostic tools necessitates a balanced and nuanced approach, considering both their strengths and limitations.

The interplay between sensitivity and specificity in Chest CT underscores the need for context-aware interpretation, especially in diverse epidemiological settings. Acknowledging the potential false positives and negatives becomes pivotal in guiding clinical decisions and resource allocation.

Similarly, the diverse landscape of biomarkers, each contributing uniquely to the prognostic puzzle, demands continued exploration. Future research endeavors should delve into the intricate dynamics of these markers, considering their potential in early identification of disease severity and subsequent clinical management.

As the global scientific community relentlessly pursues a deeper understanding of COVID-19, the findings from Chest CT and biomarker studies contribute valuable pieces to the evolving puzzle. Informed clinical decision-making, guided by a comprehensive understanding of these tools, is essential for optimizing patient care and navigating the dynamic landscape of the pandemic.

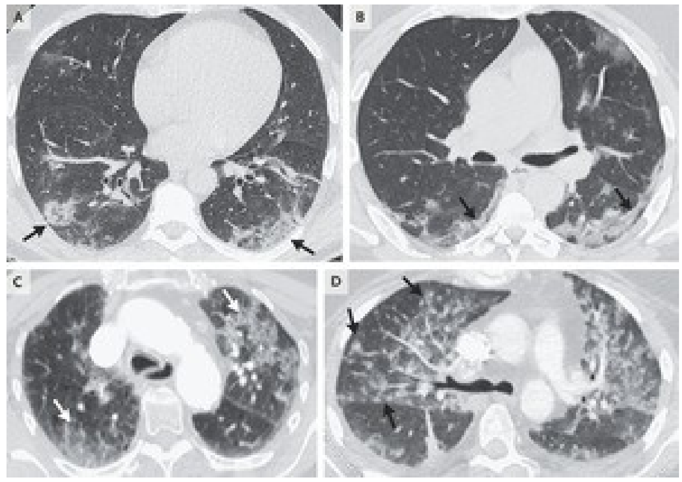

Figure 1: *Pattern of CT findings in Covid-19 patients.*[6]

Commonly reported CT findings of Covid-19 pneumonia include bilateral pulmonary opacities distributed in the peripheral lower lung and The opacities can be multifocal, are often rounded, and can have the reversed halo sign (Figure a and b), figure c shows pulmonary hemorrhage or edema, and figure d shows lobar or segmental consolidation or posterior confluent consolidation.

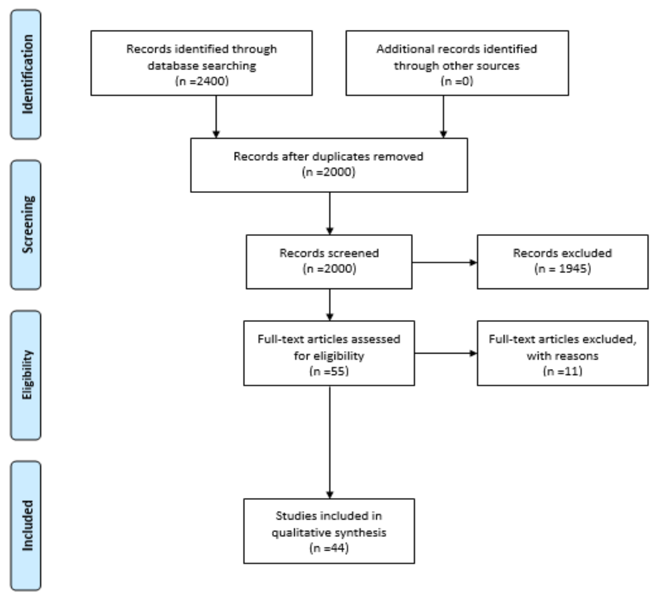

Figure 2: *Systematic review flow chart for literature refinement*

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