Effective prognostic and clinical risk stratification in COVID-19 using multimodality biomarkers

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Abstract

In acute COVID-19 patients, effective clinical risk stratification has important implications on treatment and therapeutic resource distribution. This article reviews the evidence behind a wide range of biomarkers with prognostic value in COVID-19. Patient characteristics and co-morbidities, such as cardiovascular and respiratory diseases, are associated with increased mortality risk. Peripheral oxygen saturation and arterial oxygenation are predictive of severe respiratory compromise, whilst risk scores such as the 4C-Score enable multi-factorial prognostic risk estimation. Blood tests such as markers of inflammation, cardiac injury and D-dimer, and abnormalities on electrocardiogram are linked to inpatient prognosis. Of the imaging modalities, lung ultrasound and echocardiography enable bedside assessment of prognostic abnormalities in COVID-19. Chest radiograph (CXR) and computed tomography (CT) can inform about prognostic pulmonary pathologies, whilst cardiovascular CT detects high-risk features such as coronary artery and aortic calcification. Dynamic changes in biomarkers, such as blood tests, CXR, CT and ECG findings, can further inform about disease severity and prognosis. Despite the vast volumes of existing evidence, several gaps exist in our understanding of COVID-19 biomarkers. Firstly, the pathophysiological basis on which these markers can foretell prognosis in COVID-19 remains poorly understood. Secondly, certain under-explored tests such as thoracic impedance assessment and cardiovascular magnetic resonance imaging deserve further investigation. Lastly, the prognostic value of most biomarkers in COVID-19 are derived from retrospective analyses. Prospectively studies are required to validate these markers for guiding clinical decision-making and to facilitate their translation into clinical management pathways.

Keywords: biomarker, clinical outcomes, COVID-19, diagnostic performance, prognosis, risk stratification,

Introduction

In the coronavirus disease 19 (COVID-19) pandemic, clinical risk stratification is key to effective patient management [1-4]. A major challenge faced by healthcare workers is how to differentiate patients needing urgent hospital care versus patients who could be managed in the community [1-4]. Further, in patients admitted to hospital with acute COVID-19, identifying those at a high risk of developing adverse outcomes could enable appropriate and timely delivery of therapeutic resources, which may in turn improve their prognosis [1-4].

Since 2020, numerous biomarkers have been shown to predict adverse clinical outcomes in acute COVID-19 patients [2, 4-12]. In this review, we will discuss the evidence supporting the use of these prognostic markers, current knowledge gaps and the challenges that will be faced to translate them into practical tools for clinical decision-making.

Patient characteristics

Several studies have suggested a strong link between advanced age and adverse outcomes in COVID-19 [13-19], including higher readmission rates [14], mechanical ventilation requirement [20] and mortality risk [13, 21]. Elderly patients can also present atypically, with a lower prevalence of COVID-19 related symptoms, which may in turn lead to diagnostic delays and negative prognostic implications [22].

The influence of gender on COVID-19 prognosis is controversial [19, 20, 23], likely due to a scarcity of consideration for gender differences in clinical studies [19]. Raimondi *et al*. showed that hospitalised female patients were less likely to suffer mortality overall, but in the context of severe COVID-19, there was no significant difference in mortality risk across genders [23]. Further work is needed to ascertain the true effect of gender on COVID-19 prognosis.

Smoking is associated with a higher risk of adverse outcomes in COVID-19 patients [11, 24, 25]. Data from observational studies are supported by a recent expert opinion on the deleterious effects of cigarette smoking on COVID-19 related hospitalisation and mortality [26], in line with the harms of smoking in other respiratory diseases [27].

Patient co-morbidities

The assessment of co-morbidities is important in predicting adverse outcomes from COVID-19 [13, 14, 16, 21, 28-31]. Hypertension is the commonest reported co-morbidity, affecting up to 50% of COVID-19 patients [32]. Both hypertension and pre-existing cardiovascular diseases are linked to increased risks of severe COVID-19 and mortality [31, 33-36]. Whilst some evidence suggested a protective role of pre-existing angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) administration in hypertensive patients infected with COVID-19 [37], a randomised trial showed that discontinuation of ACE inhibitors or ARBs did not significant affect prognosis [38]. Disorders of lipid metabolism are also prevalent but their association with adverse outcomes in COVID-19 is weak [32]. Further, whilst complicated diabetes mellitus is strongly linked to mortality in COVID-19 patients [32], uncomplicated diabetes confers a weaker prognostic effect [32]. Both obesity alone [32] and in combination with other co-morbidities [39] are linked to adverse clinical outcomes.

Of the respiratory co-morbidities in COVID-19 patients, chronic obstructive pulmonary disease (COPD) is the commonest, followed by asthma and bronchiectasis [40]. Having pre-existing COPD renders COVID-19 patients at a greater risk of requiring mechanical ventilation, intensive care unit (ITU) admissions [40, 41] and suffering mortality [41]. Asthma, but not bronchiectasis, is significantly associated with a higher risk of invasive ventilation, ITU admissions and mortality [40]. Moreover, patients with pre-existing respiratory diseases can suffer worse exacerbations when infected with COVID-19 [42, 43]. It remains unclear whether the increased mortality risk is due to more severe COVID-19 manifestation in the presence of respiratory co-morbidities, or worse respiratory disease exacerbations provoked by COVID-19 [40-45], or both. Further investigation is needed to better answer this question.

Bacterial coinfection is also linked to a worse prognosis in COVID-19 patients [46]. However, the prevalence of bacterial infection in COVID-19 is considered low [47] and existing evidence does not support the routine use of antibiotics in this setting [48]. There is currently no specific guidance on the diagnosis and management of bacterial coinfections in COVID-19.

Patients with underlying cancer are considered to be at a higher risk for contracting COVID-19 [49], and once infected, cancer patients are at a greater risk of ITU admissions and

mortality [50, 51]. The exact mechanisms for these elevated risks remain incompletely understood [52], which may involve molecular, cellular and immunological interactions between malignancies and acute COVID-19 [52]. Other co-morbidities such as renal disease, dementia and the human immunodeficiency virus (HIV) are also reported risk factors for mortality in COVID-19 [53].

As an overall consideration, the risk of adverse outcomes in COVID-19 patients increases with multiple co-morbidities [1, 39], since these patients have less physiological reserve when faced with infections [54]. The interaction between co-morbidities and overall mortality risk in COVID-19 remains an area of ongoing research.

Clinical observations

Several markers have been proposed for the risk stratification and management of COVID-19 patients (Figure 1).

Vital signs

Retrospective analyses showed that abnormal vital signs such as tachycardia, hypotension, increased respiratory rate and reduced oxygen saturation are linked to a higher mortality risk in COVID-19 patients [11, 55-57]. The combination of hypoxaemia and hypotension confer a particularly poor prognosis [58]. These observations are unsurprising given that abnormal vital signs are well recognised in acute respiratory distress syndromes (ARDS) [59-61], conditions which share many pathophysiological characteristics with severe COVID-19 [62].

The Early Warning Score (EWS), based on vital signs, is an accepted method for identifying patients at risk of clinical deterioration [63]. Although EWS can be extrapolated for assessing disease severity in COVID-19 [8], some important caveats exist [6]. Firstly, COVID-19 patients can develop hypoxia rapidly, which is not always accompanied by symptomatic discomfort or an increase in respiratory rate [8, 57, 64]. This "happy hypoxia" phenomenon means that patients may be objectively more unwell than their bedside appearances indicate [8, 57, 64]. Secondly, occult hypoxia may be more common in Black patients compared to Caucasians, which could hinder the identification of significant deterioration based on vital signs alone [65]. Thirdly, the EWS places an emphasis on tachycardia and hypotension as markers of septic deterioration, which are not always apparent in early or non-severe

COVID-19 [66]. However, many of these patients still go on to develop significant respiratory failure, which may not be picked up early [66].

Risk score models

Several new risk predictor models have been developed for assessing adverse outcome risks in COVID-19 [15]. However, their clinical applications have been limited [15]. A recent systematic review [15] found that most of these models are affected by bias and probably overestimated their levels of performance [15]. Furthermore, many of the novel risk prediction models have failed to outperform traditional EWS-based methods [67].

One particular risk score model, the coronavirus clinical characterisation consortium (4C) mortality score [3], has shown significant promise. The scoring system includes eight parameters: age, sex, co-morbidities, respiratory rate, oxygen saturation, consciousness level, urea level and C-reactive protein (CRP) [3]. In a large validation cohort of 22,361 patients, the 4C score achieved an area under curve (AUC) of 0.77 (95% CI: 0.76 to 0.77) for predicting mortality [3]. A low 4C score (≤3 out of 21) could rule out mortality with high confidence (negative predictive value 99%). A high 4C score (≥15 out of 21) could identify patients at a high risk of mortality (positive predictive value 62%) [3]. This model has been further validated in several countries [1, 68-73]. Whilst some studies have shown a superior prognostic value of 4C over other risk scores such as CURB-65 [74-76], others did not show such a trend [77, 78]. The direct clinical application of 4C and the changes in the scores as COVID-19 progresses in severity deserve further investigation.

Blood tests

Inflammatory markers

Like most infections, severe cases of COVID-19 can induce a systemic inflammatory response similar to that observed in septic shock [12, 29, 79-82]. Serum inflammatory markers, such as leukocyte counts and CRP, remain the cornerstone of frontline assessment of infections including COVID-19, owing to the ease by which they can be tested for, the widespread availability of the tests, associated low testing costs and clinical familiarity [12, 83, 84].

On a patient group basis, serum inflammatory markers are associated with both the severity of COVID-19 [12] and overall prognosis [84]. Patients with a pattern of elevated CRP and neutrophil counts with low lymphocyte counts have a greater risk of requiring oxygen support compared to patients with other patterns of the same markers [85]. In a meta-analysis of 83 studies, patients with severe COVID-19 exhibited higher levels of CRP, erythrocyte sedimentation rate (ESR) and procalcitonin (PCT) compared to patients with non-severe disease [86]. CRP levels were also higher in non-survivors compared to survivors [86]. Recent evidence suggest that microRNA, which can influence the inflammatory cytokine response in COVID-19, can potentially infer disease severity and progression [87]. Further, microRNA could also function as possible therapeutic target in COVID-19 [88, 89]. These promising findings deserve further clinical validation.

The observed relationship between COVID-19 severity and inflammatory markers show variations by race and gender [90-93]. In Asian and Caucasian patients, non-survivors had higher CRP levels than survivors, but no such difference was observed in patients of Black and Hispanic ethnicities [90]. Male patients demonstrated higher CRP levels than female patients [91, 94, 95] which may be related to a greater activation of the innate immunity in males, while females may have more robust T cell activation [91-93]. Despite these variations, no validated correction methods currently exist in routine clinical practice to control for them.

The question remains as to whether conventional inflammatory markers can be used to foretell the outcome for individual patients with COVID-19. Existing retrospective analyses did not suggest a high diagnostic performance of inflammatory markers for this purpose [84, 96]. Further, most of the evidence is based on hospitalised patients, with scarce data available from primary care where these markers are frequently assessed. The difference in setting is an important but often overlooked factor as variations in the prevalence of the condition of interest affects practical test performance in terms of its positive and negative predictive value. An undue dependence on measures of sensitivity and specificity allied with the assumption that tests will perform in the same way in terms of their predictive value across all levels of disease prevalence is a common and dangerous misconception. Overall, inflammatory markers may be better used in conjunction with clinical assessment, rather than alone, in the management of COVID-19.

Combination biomarkers

Combinations exploit the concept that the whole could be superior to the sum of its parts [97]. In acute COVID-19 patients, several studies have tested the feasibility of combining inflammatory markers to provide clinical risk stratification [98-101]. Lymphocyte-CRP ratio is a novel biomarker designed to predict prognosis in patients with gastro-intestinal malignancies [102]. Recent studies have demonstrated the ability of this ratio to also predict disease severity and mortality in COVID-19 [98, 99, 103]. Another example of combination biomarker is elevated neutrophil-to-lymphocyte ratio (NLR), which has been associated with severe COVID-19 [98, 99]. Further examples include platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio and eosinophil-lymphocyte ratio, all of which have been tested for prognosticating COVID-19 patients with varying degrees of success [99]. Recently, both NLR and PLR have shown prognostic value in COVID-19 patients at haemodialysis initiation [104].

The promise shown by combination biomarkers in assessing COVID-19 patients should be tempered by several drawbacks. Firstly, most of the studies validating the use of combination markers have been relatively small [98, 99]. Secondly, there is a scarcity of head-to-head comparisons between novel combination markers and conventional inflammatory markers, rendering their incremental value unclear. Thirdly, there is no standardisation of biomarker measurement; for instance, lymphocyte-CRP ratio [98] has also been expressed as CRP-lymphocyte ratio [103], which leads to different numerical values being generated and the derivation of unified cut-off values extremely difficult. Lastly, there is no prospective validation of combination biomarkers which would facilitate their translation into clinical use.

Cardiac troponins

Myocardial injury in COVID-19 is prevalent [9] and is linked to both severe disease manifestations [7, 9, 105-107] as well as poor prognosis [4, 5, 7, 9, 108]. Troponins are vital components of the cardiomyocyte contractile machinery and are released into the blood stream in the presence of myocardial injury [109, 110]. High sensitivity cardiac troponin (hs-cTn) is a serum biomarker routinely measured in the acute medical setting, which is highly

validated for the assessment of acute coronary syndromes [111]. Its interpretation in the context of COVID-19 has become an area of extensive retrospective analysis [5, 112].

On a patient group level, several studies have shown that COVID-19 patients with elevated hs-cTn have overall worse inpatient survival compared to patients with normal hs-cTn [105, 108, 113-115]. Non-fatal complications such as requirement for invasive ventilation and ICU admissions were also more prevalent in patients with elevated hs-cTn than normal [111, 112]. Despite such strong group differences, when used at a per-patient diagnostic level, an elevated hs-cTn failed to accurately predict prognosis in COVID-19 [108], which hampers its use as a stand-alone tool for assessing clinical risk.

Troponin levels are affected by factors other than myocardial injury, such as renal failure, pulmonary emboli and others [116], which may each exert a different effect on prognosis in COVID-19 patients. The interplay between direct viral myocardial insult and systemic inflammation remains incompletely understood and their relative contributions may impact on the degree of troponin elevations [117]. Moreover, COVID-19 may affect the heart in ways unrelated to conventional inflammatory disease, thus impacting on adverse outcomes beyond what is assessable by troponin [112, 118].

Further work is required to improve our understanding of the pathophysiology of cardiac troponin elevation in COVID-19 and to better characterise the troponin cut-offs for differentiating patients at the highest vs. lowest risks for adverse outcomes. These gaps in knowledge hamper the confidence with which we can prospectively validate the use of troponins in guiding clinical decision-making. Troponins therefore remain collectively an observational indicator of prognosis rather than a practical risk stratification tool in COVID-19.

B-type Natriuretic peptides (BNP)

BNP and N-terminal pro-B-type natriuretic peptides (NT-proBNP) are clinically accepted biomarkers used for the diagnosis and prognostication of patients with heart failure [119]. In COVID-19 patients, early data from the Wuhan outbreak indicated a possible prognostic value of elevated natriuretic peptides, as a surrogate for myocardial injury or strain [114, 115]. This finding was confirmed by a number of studies which found that patients with

severe COVID-19 and non-survivors had higher BNP or NT-proBNP than survivors with non-severe disease [120-128], regardless of the presence of heart failure [119, 125].

Despite the promising inter-group data, establishing a diagnostic threshold using BNP/NT-proBNP to predict adverse outcomes on an individual level is challenging [120-128]. The patient populations studied tend to be heterogeneous in admission characteristic [120-128]. Moreover, the amalgam of evidence consists mainly of retrospective analyses or single-centred prospective cohorts [120-128]. There remains no prospectively validated natriuretic peptide cut-offs to predict adverse outcomes in COVID-19. The sensitivities and specificities of various thresholds from retrospective analyses are wide ranging [124, 127]. As a result, natriuretic peptides have yet to be translated into the realms of clinical decision-making in guiding COVID-19 management.

D-dimer

Before the COVID-19 pandemic, pulmonary embolism (PE) was already a common cause of morbidity and mortality worldwide [129]. In patients with moderate or low pre-test probability, low D-dimer levels can be used to reliably rule out PE [130]. In COVID-19 patients, concomitant PE is prevalent [131, 132] and worsens prognosis [133]. Further, the pro-thrombotic nature of COVID-19 meant that patients often displayed elevated baseline D-dimer levels [134]. It was therefore important to determine whether the same pre-pandemic D-dimer thresholds still applied to patients with COVID-19 [130, 133, 135, 136]. Several studies subsequently confirmed that the same previously established criteria for ruling out PE also applied in COVID-19 patients [133, 135-137], cementing the status of D-dimer as a useful tool for this purpose.

The value of an elevated D-dimer for ruling in concomitant PE in COVID-19 patients is more controversial. A number of studies have derived higher cut-off values [138-144], above which diagnostic imaging is recommended [138-144]. However, there is considerable variability in the proposed D-dimer cut-offs (ranging from 1000 ng/ml to 2903 ng/ml) [138-146] with no published consensus on which value should be used clinically. These uncertainties are reflected in the British Thoracic Society guidelines [147] which does not recommend the routine use of high D-Dimer levels in isolation to guide decisions regarding

investigation and anticoagulation for venous thromboembolic disease in COVID-19 patients [147].

As an overall prognostic indicator in COVID-19, several studies have reported that elevated D-dimer levels are associated with severe disease [148-152] and a worse prognosis [149, 151-157]. A meta-analysis of 38,310 COVID-19 patients showed that higher D-dimer levels were also associated with a greater risk of disease progression [158]. However, the lack of clinically recommended cut-off values again means that D-dimer should only be assessed within the wider clinical context rather than in isolation [147].

Platelet biomarkers

In acute COVID-19 patients, thrombocytopenia is common on admission and during hospitalisation, and is associated with an increased risk of mortality [159-165]. Of the patients with normal admission platelet counts, those who later develop thrombocytopenia also suffer worse clinical outcomes [166]. Systemic inflammation is thought to play a major role in its pathogenesis [167], whereby thrombocytopenia forms part of a wider coagulopathy in response to activation of the innate immunity to infection [168]. More specific causes such as thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemia syndrome (HUS) may precipitate thrombocytopenia in severe COVID-19 infections, leading to a poor prognosis [169]. Drug induced thrombocytopenia, with heparin or drugs used to treat COVID-19 such as azithromycin and hydroxychloroquine, can also play a prognostic role [170].

In addition to the prognostic value of altered platelet counts, excessive platelet activation is also linked to a higher mortality risk in COVID-19 patients [171]. However, this finding might be less important than coagulopathy in assessing the progression of COVID-19 [171]. These findings deserve further investigation.

Vitamin D

Before the COVID-19 pandemic, evidence suggested that vitamin D supplementation is associated with a small protective benefit against acute respiratory infections [172]. The arrival of COVID-19 sparked both further research interest and controversies. Some studies

reported that vitamin D deficiency was linked to increased susceptibility to COVID-19 infections, longer duration of hospitalisation [173-179], and that vitamin D replacement was associated with reduced ITU requirement [180] and a better prognosis [181, 182]. Conflicting evidence also emerged suggesting neutral effects of both vitamin D deficiency and replacement in COVID-19 [183-186]. One meta-analysis found that vitamin D deficiency was associated with a higher risk of ARDS and mortality [187], whilst another meta-analysis found no significant association between vitamin D deficiency and COVID-19 susceptibility or death [183].

The controversial nature of the existing evidence is reflected in the published guidelines [188, 189]. The National Institutes of Health (NIH) indicated that there is insufficient evidence to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19 [188]. Similarly, the National Institute for Health and Care Excellence (NICE) recommended against offering vitamin D supplementation solely to prevent or treat COVID-19 [189].

Figure 2 summarises the prognostic blood tests commonly performed in COVID-19 patients.

COVID-19 disease progression and biomarker assessment

Patients with COVID-19 may progress through three broad clinical stages (Figure 3): 1) an *initial stage* when the patient becomes first infected and may display associated symptoms or remain asymptomatic [190]; 2) a *progressive stage* characterised by either pulmonary involvement or, less commonly, non-pulmonary sequelae as the first manifestation of COVID-19 [191-193]; 3) a *systemic stage* with severe complications involving ARDS [190] and/or wider inflammatory and multi-organ involvement [194].

Both the levels and dynamic changes in biomarkers in the initial, progressive and systemic stages can affect the outcome (Figure 3). Widespread screening and population-based education on symptomology meant that COVID-19 patients are detected early in the disease course [195]. The initial stage of COVID-19 includes the viral incubation period and usually last up to two weeks [196]. During this time, significant biomarker abnormalities are rarely reported [197], except for lymphopenia, which appears in early disease [164].

A few days after the initial stage, a proportion of patients enter the progressive and/or systemic stages [197]. In these stages, both elevated admission levels and progressive rises in inflammatory markers, such as CRP, ferritin, IL-6 and procalcitonin, portend adverse prognosis [84, 198, 199]. Conversely, COVID-19 survivors demonstrate recovery in these markers [84]. Similarly, levels of cytokines, such as IL-2, IL-6, IL-8, IL-10 and tumour necrosis factor alpha (TNF-α), remain elevated in non-survivors and critically ill patients as compared to survivors in whom levels can decline within 10 days of hospital admission [200].

Persistently elevated D-dimer, creatinine and cardiac troponins in non-survivors during hospitalisation suggest a transition into the progressive or systemic stage [201] with pulmonary and/or extra-pulmonary involvement and an adverse prognosis [194, 201, 202]. Indeed, evidence suggests that the peak troponin levels during hospitalisation may be a better predictor of mortality than troponin levels measured on admission [202], indicating the importance of inpatient biomarker monitoring. Dynamic changes in markers of critical illness, such as elevations in creatine kinase and development or worsening of anaemia [199], not only mark the progression towards the systemic stage, but also appear to be more common in non-survivors [199]. Figure 3 summarises the possible dynamic changes in serum biomarkers during different stages of COVID-19.

Markers of pulmonary dysfunction

Peripheral oxygen saturation

Since delaying intubation is detrimental to prognosis in severe COVID-19 [203], the use of oxygenation as a simple clinical guide is highly attractive. The target saturation range of 92-96% used in practice was derived from data in ARDS patients, in whom both low saturations (<92%) [61] and high saturations (>96%) [204] are detrimental. Reduced peripheral oxygen saturation acts as both a risk factor for intubation [205-207] and a guide to the timing of assisted ventilation [208, 209]. Moreover, after COVID-19 patients have been intubated, further declines in oxygenation continue to be predictive of mortality risk [210] and improvements in saturation readings can act as a guide to the effectiveness of prone ventilation therapy [211]. Indeed, monitoring of peripheral oxygen saturation is useful not only in prognosticating patients with severe COVID-19, but also in patients discharged from hospital to facilitate early detection of acute deteriorations [212].

Arterial oxygenation

Assessment of arterial blood gas measures may provide additional risk stratification in COVID-19 patients beyond peripheral saturation monitoring [213]. Both reduced and elevated arterial oxygen partial pressure (PaO_2) are associated with an increased risk of adverse outcomes [213]. The PaO_2/FiO_2 (the ratio of PaO_2 and inhaled oxygen fraction) is an indexed used to assess the severity of ARDS and a reduced PaO_2/FiO_2 ratio has also been linked to an adverse prognosis in COVID-19 [213]. PaO_2/FiO_2 measured soon after admission predicts the risk for prolonged hospitalisation [214] and the need for intubation [206, 215, 216].

Although both PaO_2 and PaO_2/FiO_2 are associated with requirement for intubation and artificial ventilation, controversy exists as to whether these parameters are suitable to dictate the necessity for artificial ventilation [217]. PaO_2 appears to be the most precise measure of oxygenation status [217] and PaO_2/FiO_2 forms an important part of the ARDS definition [217]. However, any intubation decision is not solely dependent upon hypoxaemia [218], rather a combination of clinical parameters including increased work of breathing, hypercapnia and threatened airway owing to reduced conscious levels [218]. Therefore, whilst arterial oxygenation is an important prognostic sign, it should be used in tandem with other clinical factors when considering the need for intubation.

Thoracic impedance

Electrical impedance tomography (EIT) is performed by placing an electrode-containing belt across the chest of a patient and assessing the changes in the thoracic impedance related to respiratory aeration [219]. A series of tomographic maps are produced that demonstrate areas of normal, maximal and non-ventilation [219]. In patients with COVID-19 and/or ARDS, EIT can be used to optimise mechanical ventilation settings, titrate peak end expiratory pressures and the effectiveness of lung recruitment manoeuvres [219-222]. There is currently limited evidence on the use of EIT to predict mortality in patients with COVID-19.

Implantable cardiac defibrillators (ICD) can assess thoracic impedance by measuring the resistance between the right ventricular lead and the device, traversing significant volumes of lung tissue [223]. Changes in thoracic impedance reflects the interstitial fluid status in

pulmonary oedema [224, 225] and has been suggested to be a possible marker of disease severity in a very small sample of COVID-19 patients [223]. These preliminary findings deserve larger scale validation. Further, the changes in thoracic impedance with progressive COVID-19 remain unknown and require further investigation.

Electrocardiogram (ECG)

ECG abnormalities are common in COVID-19 patients and are either related to underlying cardiovascular diseases or as a direct result of myocardial injury (Figure 4) [226-229].

Myocardial injury

Although ST-segment and T-wave abnormalities on ECG act as surrogate markers of myocardial injury in COVID-19 [226-229], differentiating the aetiology is often challenging. In a case series, only two thirds of COVID-19 patients with ST-segment elevation who underwent coronary angiography had obstructive epicardial coronary disease [226]. Indeed, myocardial infarction with non-obstructive coronary arteries (MINOCA) has been reported in COVID-19, and is known to affect not only adults but also children [230-233]. During invasive coronary angiography, the observation of thrombotic occlusion of otherwise normal epicardial coronary arteries [230-232] have led to the belief that these episodes are due to a hypercoagulable state in COVID-19 rather than plaque rupture events [230-232]. Further, thrombotic coronary occlusions can occur as part of a wider thromboembolic phenomenon (involving LV cavity thrombus and embolic stroke) [230], or localise only to the coronary arteries [231-233].

Acute myocarditis [229, 234, 235] and Takotsubo cardiomyopathy [228, 236] can also cause myocardial injury and ECG abnormalities. Although a number of early case reports highlighted the existence of acute myocarditis in COVID-19 as a disease entity [229, 234, 235], later studies showed that its prevalence is rare on both imaging and autopsy examinations [237, 238]. The occurrence of Takotsubo cardiomyopathy in COVID-19 remains limited to case reports [239].

Atrial arrhythmias

Atrial fibrillation (AF) and atrial flutter (AFL) are the commonest arrhythmias in COVID-19, with a combined prevalence of around 11-13% [240, 241]. COVID-19 patients with AF or AFL have higher levels of inflammation and myocardial injury markers [240]. Moreover, the presence of AF or AFL is associated with the development of severe COVID-19 and a higher risk of mortality [240-242].

Heart blocks

Higher degree heart block, including complete heart block (CHB), is rare in COVID-19 [243-249], and can present with narrow or broad QRS complex escape rhythms [243-249]. CHB tends to be reversible [243, 244, 246-248], presenting in the absence of structural heart disease [243, 244, 246-248] and does not usually require permanent pacing [243-246, 248, 249]. The severity of COVID-19 in CHB patients is varied, with some requiring vasopressor support or artificial ventilation [243, 247], some succumbing to COVID-19 [243, 247], and others making a full recovery [243, 244, 246, 249]. Most cases of CHB required observation alone [243], with temporary pacing reserved for haemodynamic instability [244, 245].

Ventricular arrhythmias

In COVID-19 patients, ventricular arrhythmias are relatively rare and account for around 6% of inpatient cardiac arrests [250, 251]; while asystole and pulseless electrical activity (PEA) are more common [252]. Several potential mechanisms may drive ventricular arrhythmias in COVID-19 [253-257]. Firstly, the systemic inflammation may exacerbate pro-arrhythmogenic activity in patients with pre-existing ischaemic cardiomyopathy, myocardial scar and a nidus for ventricular tachycardia (VT) [254]. Secondly, the COVID-19 inflammatory response can unmask clinically silent non-ischaemic cardiomyopathy, leading to VT storm [255]. Thirdly, the COVID-19 infection itself can cause acute myocarditis and/or myocardial injury leading to ventricular arrhythmias [256, 257]. There is little evidence supporting the occurrence of ventricular arrhythmias in COVID-19 patients without underlying cardiac disease or myocardial injury [258, 259].

QTc prolongation

Prolongation of the correct QT interval (QTc) on ECG can occur either in the presence [260] or absence [261] of drugs used to treat COVID-19, such as hydroxychloroquine and azithromycin [260, 261]. Moreover, COVID-19 inpatients have longer QTc compared to patients discharged from the hospital [262]. Prolonged QTc is reported as an independent predictor of mortality risk [262, 263], which increased by 8.3% for every 10 ms of QTc increment [262]. QTc prolongation may be a trigger for life-threating ventricular arrhythmias [264] or a marker of acute myocardial ischaemia [265-267]; the exact mechanism underlying its prognostic risk requires further investigation.

Prognostic value of ECG abnormalities

Retrospective analyses have identified several ECG features that are related to a worse prognosis in COVID-19 (Figure 4) [260-262, 268-273]. Low voltage QRS complexes, previously shown to confer prognostic value in non-COVID-19 myocarditis [271], are also associated with increased mortality risk in COVID-19 patients [272]. Moreover, lower heart rate variability on ECG, as a marker of vagal nerve activation, has also been linked to a greater risk of ITU admission and inpatient mortality [274]. A recent large multi-centre cohort study showed that major ECG abnormalities and sinus tachycardia (>120 beats per minute) were linked to adverse clinical outcomes in COVID-19 patients [275]. However, certain ECG findings such as AF, bundle branch block, ischaemic abnormalities and prolonged QTc were not associated with adverse clinical outcomes in this study [275], which appear to cast doubts over previous data suggesting their prognostic importance [240-242, 260-262, 268-273]. The exact mechanism underlying these differences in observation remain unclear and deserve further investigation.

The assessment of the dynamic changes in ECG during hospital admissions is also important [269]. Both abnormal ECG features identified on admission [269, 270] as well as after 7 days post-admission [269] are associated with inpatient mortality and/or requirement for invasive mechanical ventilation [269, 270].

Despite the emerging evidence, there remains no consensus on how ECG findings should be used to guide clinical decisions in COVID-19. Recent work suggests the potential utilisation

of ECG abnormalities in risk scoring systems to predict mortality in COVID-19 [276]; this area deserves further exploration.

Imaging modalities

Chest Radiograph (CXR)

The use of CXR to diagnose COVID-19 is not recommended over laboratory testing by polymerase chain reaction (PCR) based methods [277, 278]. Indeed, qualitative interpretation of CXR achieved only moderate diagnostic performance for detecting COVID-19 when referenced to PCR tests [277]. However, CXR remains one of the most important frontline tests for assessing COVID-19 severity [279]. Whilst patients can present with a normal chest CXR, the commonest signs of COVID-19 are ground-glass opacifications and consolidation [279], which are most frequently distributed bilaterally, peripherally or basally [279].

CXR findings in COVID-19 are also time-dependent [280]. Ground-glass opacification can progress to consolidation at around 6-11 days since symptom onset [280]. Consolidations may later regress to ground-glass opacifications at 12-17 days [280]. The density and extent of CXR opacities peak around 10-13 days into the illness [281]. Although normal CXR is more prevalent during the recovery phase (>18 days) [280], the majority of patients have residual CXR abnormalities at discharge [281]. In some cases, prolonged hospitalisation and protracted recovery can also lead to persistence of CXR abnormalities and delayed resolution [282].

Semi-quantitative CXR interpretation, such as using the radiographic assessment of lung oedema (RALE) score, can predict clinical outcomes in critically ill patients [283] and ARDS sufferers [284]. For assessing COVID-19, semi-quantitative CXR analysis is a reproducible method with excellent inter-observer variability [285, 286]. The lung field is usually divided into discrete zones, whereby each zone is scored according to the severity of abnormalities present [284, 287, 288]. An overall severity score is derived from the sum of the zonal scores [283, 285, 289]. The number of zones implemented varies within the literature, ranging from three (upper, middle and lower) [290], to four (the RALE score) [284, 291, 292] to six (the Brixia score) [288, 289].

Elevated semi-quantitative severity scores on CXR are associated with a greater risk of COVID-19 related ITU admissions and/or inpatient mortality [283, 285, 286, 288, 289, 292, 293]. Both RALE and Brixia systems can reliably predict adverse outcomes [286]. Further, the percentage opacification on CXR, as assessed visually, also performed well for predicting the risk for ITU admission and mortality [286]. Recently, the use of artificial intelligence (AI) to provide automated CXR severity scoring has received interest [294-296]. Some studies suggest that AI performs similarly to [294], or even better than [295], human scoring for predicting clinical outcomes [294, 295]. AI-based tools may become a useful future adjunct for the assessment of COVID-19 patients [296], and rigorous prospective validation is required to translate it into the forefront of clinical practice.

Chest computed tomography (CT)

Common chest CT findings in COVID-19 include bilateral ground-glass opacifications and lower lobe consolidation [297-300], while pleural effusion, pericardial effusion and lymphadenopathy are rarer [297, 298]. Severe disease may exhibit large and multi-focal ground-glass opacifications or consolidation [297, 301]. CT features linked to a worse prognosis in COVID-19 include diffuse opacification or peripherally distributed ground-glass opacifications [302, 303], consolidation [304], anterior and para-cardiac involvement [302], the "crazy paving pattern" [302, 305], and pleural effusions [302]. More extensive opacifications involving multiple zones of the lung field and air bronchograms are also helpful in predicting adverse clinical outcomes [304].

Both the presence of abnormalities such as ground glass opacification, consolidation and fibrosis [206], and their widespread extent [304, 306] are associated with a greater risk of intubation requirement and inpatient mortality [206, 306]. Whilst the prevalence of ground glass changes falls with advancing patient age [307], pleural effusion becomes more common in elderly COVID-19 sufferers in whom it acts as a distinctive marker of mortality [307].

Dynamic changes in chest CT abnormalities in COVID-19 is important in assessing disease progression [308-310]. Abnormalities found on admission remain stable in only about a quarter of cases, with the majority progressing to a peak intensity before improving with disease resolution [308]. Maximal lung involvement on chest CT peaks at around 6-11 days from symptom onset [297, 309, 311], which appears similar to the timing of the peak appearances of opacities on CXR [281]. However, evidence suggests that CT can detect lung

abnormalities in the early stages of COVID-19 that are undetectable on CXR [297]. Further, COVID-19 related changes can be evident in asymptomatic patients on CT [297].

On chest CT imaging, ground-glass opacifications appear early in the disease process, usually apparent within a few days of symptom onset [311]. Other signs such as the "crazy paving pattern" and lung consolidations tend to appear later, around 1-2 weeks into the illness [311]. Gradual resolution of chest CT abnormalities may begin to occur 2 weeks after onset of symptoms [311], with residual abnormalities being present in the majority of patients at the time of hospital discharge [309]. Of the progressive chest CT abnormalities, those consistent with ARDS are most likely associated with ITU admissions and mortality [297].

Main pulmonary artery (MPA) dilation on chest CT is associated with myocardial injury and mortality in acute COVID-19 [312, 313]. Measurement of MPA diameter on CT images is simple to perform and reproducible [312]. MPA dilation is an early feature in COVID-19 [314] and constitutes a marker of pulmonary hypertension, which may be related to microvascular thrombosis, ARDS and lung injury [312]. Other features of pulmonary hypertension associated with adverse outcomes include septal flattening and IVC contrast reflux [315], which may be related to right ventricular failure and/or ventilation perfusion mismatch [312].

Figure 5 illustrates the evaluation of respiratory complications.

Cardiovascular CT

The presence of coronary artery calcification (CAC), defined as areas with >130 Hounsfield units on CT, is linked to a composite of non-invasive and invasive ventilation, extracorporeal membrane oxygenation, or mortality [316]. In COVID-19 patients with hypertension, CAC is associated with inpatient mortality independent of other common risk factors such as age and diabetes [317]. A recent meta-analysis involving 4542 patient showed that patients with high CAC scores (≥300) were more likely to suffer mortality than patients with low CAC scores (0-299) [318]. Conversely, the absence of CAC has a high negative predictive value for ruling out major cardiovascular events in COVID-19 [313, 319].

The pathophysiological basis for the association between CAC and adverse outcomes in COVID-19 remains unclear. When age was adjusted in one study, the link between CAC and

prognosis became non-significant [320]. Moreover, elevated CAC score did not predict myocardial injury in COVID-19 patients [313]. Indeed, there is little direct evidence linking CAC to myocardial infarction in COVID-19 patients, which is preferentially related to a prothrombotic state rather than plaque rupture events [318]. CAC also has little or no predictive power on ITU admissions, which is likely multi-factorial [318].

In COVID-19 patients who suffered adverse clinical outcomes, it remains unclear whether the degree of coronary calcification remained stable, owing to a paucity of serial CT scanning studies during the acute illness. Moreover, the degree of pre-existing coronary calcification is often unknown and difficult to elucidate in retrospective studies. Therefore, further work is needed to elucidate the mechanism underlying the prognostic value of CAC in COVID-19.

Aortic calcification is reportedly more prevalent in non-surviving COVID-19 patients than survivors [321] and the presence of aortic calcification is linked to adverse clinical outcomes [315, 321]. However, the mechanism underlying this observation is poorly understood. The occurrence of aortic dissection in acute COVID-19 patients is relatively rare [322] and any potential link to aortic calcification is tenuous. Calcification of the aortic valve is also more pronounced in non-surviving COVID-19 patients but does not predict adverse clinical outcomes [321]. There is no direct evidence linking aortic valve calcification and valvular dysfunction in COVID-19.

The broader clinical applications of cardiovascular CT in COVID-19 are wide-ranging, including assessment of patients with chest pain, elevated cardiac troponins of unclear aetiology, possible intra-cardiac thrombi and for planning of urgent valvular interventions [323]. The use of cardiovascular CT has reportedly increased during the pandemic in certain centres, possibly owing to the reduced availability of other non-invasive imaging modalities; the desire to avoid invasive coronary angiography; and the option to adapt imaging protocols to include full chest CT studies in the same sitting [323].

Lung ultrasound

The advantages of lung ultrasound examination, namely its bedside-ready, non-invasive, non-irradiating and rapid-turnover characteristics, helped to propel it to the pandemic frontline [324-329]. Lung ultrasound aids in both the diagnosis of COVID-19 pneumonia and the assessment of disease severity [326-328]. Adverse sonographic features in COVID-19

include pleural line thickening and irregularity; B lines (a manifestation of interstitial oedema and ground glass opacities on CT); consolidations; and pleural effusions [326, 328, 330, 331]. Many of these are present in both COVID-19 and other types of pneumonia [332].

High risk lung ultrasound findings such as large confluent B lines, consolidations and bilateral involvement are associated with prolonged hospitalisation, the need for intensive respiratory support and ITU admissions [329]. An elevated lung ultrasound score, based on the number and severity of abnormalities, is associated not only with a heightened risk of invasive ventilation requirement [325] and mortality [324], but also with abnormalities of other markers of prognosis, such as elevated CRP, D-dimer, troponin and creatine kinase [324]. Further, patients with persisting adverse features on repeat lung ultrasound examinations are more likely to suffer clinical deterioration, likely related to the loss of aeration in lung segments [325].

Transthoracic echocardiography (TTE)

In both critical and non-critical care settings, TTE is considered a frontline cardiovascular imaging tool in COVID-19 [333-339]. Abnormal TTE findings are common and alter clinical management in up to one third of cases [333, 334]. Assessment of ventricular dysfunction enables the diagnosis of heart failure [333, 340], in particular RV failure in the context of COVID-19 pneumonia, pulmonary embolism and/or mechanical ventilation [341]. Observational data suggest that ventricular dysfunction, in particular acute cor pulmonale [341], is associated with a poor prognosis in acute COVID-19 [339, 341, 342]. TTE also assists in the detection of cardiac injury related to myocardial infarction, myocarditis and Takotsubo cardiomyopathy [333-339].

The potential clinical benefit of diagnostic TTE is balanced against the tangible risks of operator exposure to acute COVID-19 and equipment contamination [340]. As a result, echocardiography examination is recommended in acute COVID-19 patients if the information obtained is likely to lead to a clinical benefit [340]. Where possible, focused studies using smaller portable machines are recommended to reduce scan time and increase the ease of decontamination [340].

Despite emerging evidence on the use of TTE in COVID-19 patients, the effect of disease progression on TTE findings remains unclear. For instance, it is unclear at which stage of

COVID-19 infection that cardiac dysfunction develops in patients. Further work is therefore needed in this area to enable timely delivery of therapy.

The potential usefulness of clinical assessment and biomarkers for each stage of the acute COVID-19 infection is shown in Figure 6.

Cardiovascular Magnetic Resonance (CMR)

CMR offers multi-parametric assessment of cardiac structure, function and myocardial tissue characterisation [343, 344]. Although the routine use of CMR to assess acute COVID-19 patients has been limited [235], owing to logistic and infection control issues, several studies have used CMR to characterise convalescent COVID-19 survivors, shedding light on the pattern of myocardial injury that might have taken place during the acute infective phase [107, 237, 345-348]. COVID-19 survivors can exhibit left and/or right ventricular dysfunction [107, 346], both ischaemic and non-ischaemic patterns of late gadolinium enhancement (LGE) [107, 346, 348], pericardial enhancement [346], myocardial ischaemia [107] and microvascular dysfunction [349]. The prognostic value of these abnormalities in acute COVID-19 remains unclear. There is currently limited evidence supporting the use of CMR to directly guide frontline clinical decision-making in acute COVID-19, which is an area of further research. Moreover, the limited use of CMR during acute COVID-19 meant that it is unknown at which stage of the infection myocardial injury and oedema take place, which hinders early therapy for these patients. Additional studies involving serial scans during the acute infection would address this knowledge gap.

Future perspectives

Acute COVID-19: a perpetual health problem

As SARS-CoV-2 mutates [350, 351], new strains will continue to emerge, leading to further surges in hospitalisation rates and mortality worldwide [350, 351]. Vaccination programs offers effective protection to selected populations [352, 353], although immunity is not permanent, and vaccinated individuals continue to play a role in transmission. Unvaccinated populations remain vulnerable [354]. Population-based infection control strategies, such as mask-wearing, lock-downs and social distancing, are effective in slowing the rates of

transmission but increasingly tend to be a reactive response to viral surges which are variably tolerated by the mandated populations [355]. Acute COVID-19 will likely remain a significant healthcare problem in the foreseeable future. Effective prognostic markers that can guide patient management will always be required.

Transition in evidence

Despite the extensive retrospective data on COVID-19 biomarkers, their transition into clinical guidelines has yet to materialise. Promising biomarkers such as troponins and BNP [108, 115, 121] need to be prospectively validated for guiding clinical decision-making. These new data are crucial for the development of management pathways. Novel biomarkers, both on a cellular level, such as markers of lymphocyte apoptosis [356], and on a molecular level, such as interleukin 8 [357], interleukin-17, plasminogen activator inhibitors [356], microRNA [87] and gene expression tests [358], could enrich the repertoire of tests available to clinicians in the future.

Emergence of COVID-19 therapies such as dexamethasone [359] and Remdesivir [360] in the early trials have set a benchmark for more recent therapeutic advances [361, 362]. Targeting these treatments to patients most in need of them rely on there being accurate clinical risk stratification tools. Future clinical services that integrate artificial intelligence biomarker analysis could provide both speed and accuracy in assisting the clinician in managing COVID-19 patients. This is an exciting future direction.

Long-COVID

Up to 30% of acute COVID-19 survivors develop "long-COVID", with symptoms persisting long after the acute infection has subsided [363, 364]. Although the risk of developing long-COVID is lower with the recent Omicron variant [365], vaccination offers only partial protection [366, 367]. Long-COVID patients suffer reduced quality of life [368], repeated hospitalisations [369] and impaired prognosis [369]. Improving risk stratification and targeted therapeutic delivery in the acute setting may help to reduce the prevalence and severity of long-COVID; but this remains speculative. Further work is needed to understand the cellular and molecular pathophysiological march from acute COVID-19 to long-COVID.

Conclusion

A number of frontline biomarkers have prognostic value in COVID-19 patients. Patients are often asymptomatic during the initial incubation stage, when clinical tests are unremarkable, and risk-stratification relies mainly on patient characteristics and co-morbidities. As COVID-19 enters the progressive stage, patients can become symptomatic and present to medical services. Deranged vital signs, arterial oxygenation, and elevated serum biomarkers such as CRP, cardiac troponins and D-dimer, have shown some evidence for prognosticating clinical outcomes. Imaging abnormalities on CXR, chest CT and lung ultrasound may further assess disease severity and prognosis. ECG abnormalities can provide clues as to a patient's overall risk and echocardiography can detect cardiac dysfunction. More work is needed to elucidate the usefulness of tests such as thoracic impedance, cardiac CT and CMR for assessing acute COVID-19. In the systemic stage, when the infection may be severe, persistence or worsening of biomarker abnormalities observed in the progressive stage may portend a poor prognosis. However, this is an area that requires further investigation. Finally, caution should be exercised regarding any reliance on the use of biomarkers to assess prognosis in COVID-19 since the majority of evidence is retrospective and prospective validation is required for their clinical translation.

Conflict of interest

Prof Juan Carlos Kaski declared receipt of speaker fees from Menarini Farmaceutical SRL and Servier France. All other authors declare no conflict of interest in relation to this manuscript.

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References

1 Ali R, Qayyum F, Ahmed N*, et al.* Isaric 4c Mortality Score As A Predictor Of In-Hospital Mortality In Covid-19 Patients Admitted In Ayub Teaching Hospital During First Wave Of The Pandemic. *J Ayub Med Coll Abbottabad* 2021; **33:** 20-5.

2 Campbell TW, Wilson MP, Roder H*, et al.* Predicting prognosis in COVID-19 patients using machine learning and readily available clinical data. *Int J Med Inform* 2021; **155:** 104594.

3 Knight SR, Ho A, Pius R*, et al.* Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. *BMJ* 2020; **370:** m3339.

4 Lorente-Ros A, Monteagudo Ruiz JM, Rincon LM*, et al.* Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. *Cardiol J* 2020.

5 Bavishi C, Bonow RO, Trivedi V, Abbott JD, Messerli FH, Bhatt DL. Acute myocardial injury in patients hospitalized with COVID-19 infection: A review. *Prog Cardiovasc Dis* 2020.

6 Bradley P, Frost F, Tharmaratnam K, Wootton DG, Research NWCOfR. Utility of established prognostic scores in COVID-19 hospital admissions: multicentre prospective evaluation of CURB-65, NEWS2 and qSOFA. *BMJ Open Respir Res* 2020; **7**.

7 Cosyns B, Lochy S, Luchian ML*, et al.* The role of cardiovascular imaging for myocardial injury in hospitalized COVID-19 patients. *Eur Heart J Cardiovasc Imaging* 2020; **21:** 709-14.

8 Coughlan C, Rahman S, Honeyford K, Costelloe CE. Developing useful early warning and prognostic scores for COVID-19. *Postgrad Med J* 2021; **97:** 477-80.

9 Guo T, Fan Y, Chen M*, et al.* Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020.

10 Gupta RK, Harrison EM, Ho A*, et al.* Development and validation of the ISARIC 4C Deterioration model for adults hospitalised with COVID-19: a prospective cohort study. *Lancet Respir Med* 2021; **9:** 349-59.

11 Izcovich A, Ragusa MA, Tortosa F*, et al.* Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *PLoS One* 2020; **15:** e0241955.

12 Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, Deng G. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. *Int J Infect Dis* 2020; **96:** 467-74.

13 Yang X, Yu Y, Xu J*, et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8:** 475-81.

14 Richardson S, Hirsch JS, Narasimhan M*, et al.* Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *Jama* 2020; **323:** 2052-9.

15 Wynants L, Van Calster B, Collins GS*, et al.* Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ* 2020; **369:** m1328.

16 Romero Starke K, Petereit-Haack G, Schubert M, Kämpf D, Schliebner A, Hegewald J, Seidler A. The Age-Related Risk of Severe Outcomes Due to COVID-19 Infection: A Rapid Review, Meta-Analysis, and Meta-Regression. *Int J Environ Res Public Health* 2020; **17**.

17 Jain V, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. *Int J Public Health* 2020; **65:** 533-46.

18 Figliozzi S, Masci PG, Ahmadi N*, et al.* Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis. *Eur J Clin Invest* 2020; **50:** e13362.

19 Brady E, Nielsen MW, Andersen JP, Oertelt-Prigione S. Lack of consideration of sex and gender in COVID-19 clinical studies. *Nat Commun* 2021; **12:** 4015.

20 Ioannou GN, Locke E, Green P*, et al.* Risk Factors for Hospitalization, Mechanical Ventilation, or Death Among 10 131 US Veterans With SARS-CoV-2 Infection. *JAMA Netw Open* 2020; **3:** e2022310.

21 Chen T, Dai Z, Mo P, *et al.* Clinical Characteristics and Outcomes of Older Patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: A Single-Centered, Retrospective Study. *J Gerontol A Biol Sci Med Sci* 2020; **75:** 1788-95.
22 Unim B, Palmieri L, Lo Noce C, Brusaferro S, Onder G. Prevalence of COVID-19-related symptoms by age group. *Aging Clin Exp Res* 2021; **33:** 1145-7.
23 Raimondi F, Novelli L, Ghirardi A, *et al.* Covid-19 and gender: lower rate but same mortality of severe disease in women—an observational study. *BMC Pulmonary Medicine* 2021; **21:** 96.
24 Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. *Tob Induc Dis* 2020; **18:** 20.
25 Shastri MD, Shukla SD, Chong WC, *et al.* Smoking and COVID-19: What we know so far. *Respir Med* 2021; **176:** 106237.
26 Benowitz NL, Goniewicz ML, Halpern-Felsher B, *et al.* Tobacco product use and the risks of SARS-CoV-2 infection and COVID-19: current understanding and recommendations for future research. *The Lancet Respiratory Medicine* 2022; **10:** 900-15.
27 Grigg J. Smoking, nicotine, and COVID-19. *The Lancet Respiratory Medicine* 2022; **10:** 818-9.
28 Chen J, Liu Y, Qin J, *et al.* Hypertension as an independent risk factor for severity and mortality in patients with COVID-19: a retrospective study. *Postgraduate Medical Journal* 2021**:** postgradmedj-2021-140674.
29 Elezkurtaj S, Greuel S, Ihlow J, *et al.* Causes of death and comorbidities in hospitalized patients with COVID-19. *Sci Rep* 2021; **11:** 4263.
30 Kabbaha S, Al-Azzam S, Karasneh RA, *et al.* Predictors of invasive mechanical ventilation in hospitalized COVID-19 patients: a retrospective study from Jordan. *Expert Review of Respiratory Medicine* 2022; **16:** 945-52.
31 Gold MS, Sehayek D, Gabrielli S, Zhang X, McCusker C, Ben-Shoshan M. COVID-19 and comorbidities: a systematic review and meta-analysis. *Postgrad Med* 2020; **132:** 749-55.
32 Kompaniyets L, Pennington AF, Goodman AB, *et al.* Underlying Medical Conditions and Severe Illness Among 540,667 Adults Hospitalized With COVID-19, March 2020-March 2021. *Prev Chronic Dis* 2021; **18:** E66.
33 Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. *Arch Acad Emerg Med* 2020; **8:** e35.
34 Zuin M, Rigatelli G, Zuliani G, Rigatelli A, Mazza A, Roncon L. Arterial hypertension and risk of death in patients with COVID-19 infection: Systematic review and meta-analysis. *J Infect* 2020; **81:** e84-e6.
35 Zhou F, Yu T, Du R, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet* 2020; **395:** 1054-62.
36 Guan WJ, Liang WH, Zhao Y, *et al.* Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020; **55**.
37 Meng J, Xiao G, Zhang J, *et al.* Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect* 2020; **9:** 757-60.
38 Lopes RD, Macedo AVS, de Barros E Silva PGM, *et al.* Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial. *JAMA* 2021; **325:** 254-64.
39 Al Heialy S, Hachim MY, Hachim IY, *et al.* Combination of obesity and co-morbidities leads to unfavorable outcomes in COVID-19 patients. *Saudi J Biol Sci* 2021; **28:** 1445-50.
40 Guan WJ, Liang WH, Shi Y, Gan LX, Wang HB, He JX, Zhong NS. Chronic Respiratory Diseases and the Outcomes of COVID-19: A Nationwide Retrospective Cohort Study of 39,420 Cases. *J Allergy Clin Immunol Pract* 2021; **9:** 2645-55.e14.
41 Lee SC, Son KJ, Han CH, Park SC, Jung JY. Impact of COPD on COVID-19 prognosis: A nationwide population-based study in South Korea. *Scientific Reports* 2021; **11:** 3735.
42 Suliman AM, Bitar BW, Farooqi AA, Elarabi AM, Aboukamar MR, Abdulhadi AS. COVID-19-Associated Bronchiectasis and Its Impact on Prognosis. *Cureus*. 2021; e15051.

43 Graziani D, Soriano JB, Del Rio-Bermudez C*, et al.* Characteristics and Prognosis of COVID-19 in Patients with COPD. *J Clin Med* 2020; **9**.
44 Tan JY, Conceicao EP, Wee LE, Sim XYJ, Venkatachalam I. COVID-19 public health measures: a reduction in hospital admissions for COPD exacerbations. *Thorax* 2021; **76:** 512-3.
45 Crichton ML, Shoemark A, Chalmers JD. The Impact of the COVID-19 Pandemic on Exacerbations and Symptoms in Bronchiectasis: A Prospective Study. *Am J Respir Crit Care Med* 2021; **204:** 857-9.
46 Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. *PLOS ONE* 2021; **16:** e0251170.
47 Langford BJ, So M, Raybardhan S*, et al.* Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2020; **26:** 1622-9.
48 Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *The Journal of infection* 2020; **81:** 266-75.
49 Patel R, Park J, Shah A, Saif MW. COVID-19 and Cancer Patients. *Cancer Med J* 2020; **3:** 40-8.
50 Yang L, Chai P, Yu J, Fan X. Effects of cancer on patients with COVID-19: a systematic review and meta-analysis of 63,019 participants. *Cancer Biol Med* 2021; **18:** 298-307.
51 Giannakoulis VG, Papoutsi E, Siempos II. Effect of Cancer on Clinical Outcomes of Patients With COVID-19: A Meta-Analysis of Patient Data. *JCO Global Oncology* 2020**:** 799-808.
52 Sinha S, Kundu CN. Cancer and COVID-19: Why are cancer patients more susceptible to COVID-19? *Med Oncol* 2021; **38:** 101.
53 Sanyaolu A, Okorie C, Marinkovic A*, et al.* Comorbidity and its Impact on Patients with COVID-19. *SN Compr Clin Med* 2020; **2:** 1069-76.
54 McDermid RC, Bagshaw SM. 303Physiological Reserve and Frailty in Critical Illness. In: Stevens RD, Hart N, Herridge MS, eds, *Textbook of Post-ICU Medicine: The Legacy of Critical Care*: Oxford University Press. 2014; 0.
55 Rechtman E, Curtin P, Navarro E, Nirenberg S, Horton MK. Vital signs assessed in initial clinical encounters predict COVID-19 mortality in an NYC hospital system. *Sci Rep* 2020; **10:** 21545.
56 Xie J, Covassin N, Fan Z*, et al.* Association Between Hypoxemia and Mortality in Patients With COVID-19. *Mayo Clin Proc* 2020; **95:** 1138-47.
57 Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. *Respir Res* 2020; **21:** 198.
58 Sun B, Wang H, Lv J, Pei H, Bai Z. Predictors of Mortality in Hospitalized COVID-19 Patients Complicated With Hypotension and Hypoxemia: A Retrospective Cohort Study. *Front Med (Lausanne)* 2021; **8:** 753035.
59 Vincent JL. The Clinical Challenge of Sepsis Identification and Monitoring. *PLoS Med* 2016; **13:** e1002022.
60 Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013; **369:** 840-51.
61 Barrot L, Asfar P, Mauny F*, et al.* Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. *N Engl J Med* 2020; **382:** 999-1008.
62 Beltran-Garcia J, Osca-Verdegal R, Pallardo FV*, et al.* Sepsis and Coronavirus Disease 2019: Common Features and Anti-Inflammatory Therapeutic Approaches. *Crit Care Med* 2020; **48:** 1841-4.
63 Gerry S, Bonnici T, Birks J, Kirtley S, Virdee PS, Watkinson PJ, Collins GS. Early warning scores for detecting deterioration in adult hospital patients: systematic review and critical appraisal of methodology. *BMJ* 2020; **369:** m1501.
64 Haryalchi K, Heidarzadeh A, Abedinzade M, Olangian-Tehrani S, Ghazanfar Tehran S. The Importance of Happy Hypoxemia in COVID-19. *Anesth Pain Med* 2021; **11:** e111872.
65 Valbuena VSM, Barbaro RP, Claar D*, et al.* Racial Bias in Pulse Oximetry Measurement Among Patients About to Undergo Extracorporeal Membrane Oxygenation in 2019-2020: A Retrospective Cohort Study. *Chest* 2021.
66 Brusasco C, Corradi F, Di Domenico A*, et al.* Continuous positive airway pressure in COVID-19 patients with moderate-to-severe respiratory failure. *Eur Respir J* 2021; **57**.

67 Gupta RK, Marks M, Samuels THA, *et al.* Systematic evaluation and external validation of 22 prognostic models among hospitalised adults with COVID-19: an observational cohort study. *Eur Respir J* 2020; **56**.
68 Jones A, Pitre T, Junek M, *et al.* External validation of the 4C mortality score among COVID-19 patients admitted to hospital in Ontario, Canada: a retrospective study. *Sci Rep* 2021; **11:** 18638.
69 Kuroda S, Matsumoto S, Sano T, *et al.* External validation of the 4C Mortality Score for patients with COVID-19 and pre-existing cardiovascular diseases/risk factors. *BMJ Open* 2021; **11:** e052708.
70 Mohamed RAE, Abdelsalam EM, Maghraby HM, Al Jedaani HS, Rakha EB, Hussain K, Sultan I. Performance features and mortality prediction of the 4C Score early in COVID-19 infection: a retrospective study in Saudi Arabia. *J Investig Med* 2022; **70:** 421-7.
71 Sawczynska K, Wnuk M, Jagiella J, *et al.* 4C Mortality Score correlates with in-hospital functional outcome after COVID-19-associated ischaemic stroke. *Neurol Neurochir Pol* 2021; **55:** 295-9.
72 Ong SWX, Sutjipto S, Lee PH, *et al.* Validation of ISARIC 4C mortality and deterioration scores in a mixed vaccination status cohort of hospitalized COVID-19 patients in Singapore. *Clin Infect Dis* 2022.
73 Morello F, Bima P, Giamello JD, *et al.* A 4C mortality score based dichotomic rule supports Emergency Department discharge of COVID-19 patients. *Minerva Med* 2022.
74 Ocho K, Hagiya H, Hasegawa K, Fujita K, Otsuka F. Clinical Utility of 4C Mortality Scores among Japanese COVID-19 Patients: A Multicenter Study. *J Clin Med* 2022; **11**.
75 Martin J, Gaudet-Blavignac C, Lovis C, *et al.* Comparison of prognostic scores for inpatients with COVID-19: a retrospective monocentric cohort study. *BMJ Open Respiratory Research* 2022; **9:** e001340.
76 Innocenti F, De Paris A, Lagomarsini A, *et al.* Stratification of patients admitted for SARS-CoV2 infection: prognostic scores in the first and second wave of the pandemic. *Internal and Emergency Medicine* 2022.
77 Citu C, Gorun F, Motoc A, *et al.* Evaluation and Comparison of the Predictive Value of 4C Mortality Score, NEWS, and CURB-65 in Poor Outcomes in COVID-19 Patients: A Retrospective Study from a Single Center in Romania. *Diagnostics* 2022; **12:** 703.
78 Doğanay F, Ak R. Performance of the CURB-65, ISARIC-4C and COVID-GRAM scores in terms of severity for COVID-19 patients. *Int J Clin Pract* 2021; **75:** e14759.
79 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, Hlh Across Speciality Collaboration UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395:** 1033-4.
80 Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; **20:** 363-74.
81 Wong RSY. Inflammation in COVID-19: from pathogenesis to treatment. *Int J Clin Exp Pathol* 2021; **14:** 831-44.
82 Ramos-Casals M, Brito-Zeron P, Mariette X. Systemic and organ-specific immune-related manifestations of COVID-19. *Nat Rev Rheumatol* 2021; **17:** 315-32.
83 Faix JD. Biomarkers of sepsis. *Crit Rev Clin Lab Sci* 2013; **50:** 23-36.
84 Parimoo A, Biswas A, Baitha U, *et al.* Dynamics of Inflammatory Markers in Predicting Mortality in COVID-19. *Cureus* 2021; **13:** e19080.
85 Lee EE, Song KH, Hwang W, *et al.* Pattern of inflammatory immune response determines the clinical course and outcome of COVID-19: unbiased clustering analysis. *Sci Rep* 2021; **11:** 8080.
86 Mahat RK, Panda S, Rathore V, Swain S, Yadav L, Sah SP. The dynamics of inflammatory markers in coronavirus disease-2019 (COVID-19) patients: A systematic review and meta-analysis. *Clin Epidemiol Glob Health* 2021; **11:** 100727.
87 Mohamed HA, Abdelkafy AE, Khairy RMM, Abdelraheim SR, Kamel BA, Marey H. MicroRNAs and cytokines as potential predictive biomarkers for COVID-19 disease progression. *Sci Rep* 2023; **13:** 3531.
88 Srivastava S, Garg I, Singh Y, *et al.* Evaluation of altered miRNA expression pattern to predict COVID-19 severity. *Heliyon* 2023; **9:** e13388.

89 Fani M, Zandi M, Ebrahimi S, Soltani S, Abbasi S. The role of miRNAs in COVID-19 disease. 2021; **16:** 301-6.
90 Go RC, Nyirenda T, Bojarian M*, et al.* Racial/ethnic disparities on inflammation and response to methylprednisolone in severe COVID-19 pneumonia. *BMC Infect Dis* 2022; **22:** 254.
91 Cheng R, Liu C, Yang J*, et al.* Sex Differences in the Incidence and Risk Factors of Myocardial Injury in COVID-19 Patients: A Retrospective Cohort Study. *Front Physiol* 2021; **12:** 632123.
92 Qi S, Ngwa C, Morales Scheihing DA*, et al.* Sex differences in the immune response to acute COVID-19 respiratory tract infection. *Biol Sex Differ* 2021; **12:** 66.
93 Takahashi T, Ellingson MK, Wong P*, et al.* Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature* 2020; **588:** 315-20.
94 Lau ES, McNeill JN, Paniagua SM*, et al.* Sex differences in inflammatory markers in patients hospitalized with COVID-19 infection: Insights from the MGH COVID-19 patient registry. *PLoS One* 2021; **16:** e0250774.
95 Zhao G, Xu Y, Li J, Cui X, Tan X, Zhang H, Dang L. Sex differences in immune responses to SARS-CoV-2 in patients with COVID-19. *Biosci Rep* 2021; **41**.
96 Barrett B, Pamphile S, Yang F*, et al.* Inflammatory markers are poorly predictive of clinical outcomes among hospitalized patients with COVID-19. *Am J Emerg Med* 2021; **46:** 595-8.
97 Coates ARM, Hu Y, Holt J, Yeh P. Antibiotic combination therapy against resistant bacterial infections: synergy, rejuvenation and resistance reduction. *Expert Rev Anti Infect Ther* 2020; **18:** 5-15.
98 Ullah W, Basyal B, Tariq S*, et al.* Lymphocyte-to-C-Reactive Protein Ratio: A Novel Predictor of Adverse Outcomes in COVID-19. *Journal of Clinical Medicine Research; Vol 12, No 7, Jul 2020* 2020.
99 Damar Çakırca T, Torun A, Çakırca G, Portakal RD. Role of NLR, PLR, ELR and CLR in differentiating COVID-19 patients with and without pneumonia. *International Journal of Clinical Practice* 2021; **75:** e14781.
100 Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *Journal of Medical Virology* 2020; **92:** 1733-4.
101 Nooh HA, Abdellateif MS, Refaat L, Kandeel EZ, Bayoumi A, Samra M, Khafagy M. The role of inflammatory indices in the outcome of COVID-19 cancer patients. *Medical Oncology* 2021; **39:** 6.
102 Okugawa Y, Toiyama Y, Yamamoto A*, et al.* Lymphocyte-C-reactive Protein Ratio as Promising New Marker for Predicting Surgical and Oncological Outcomes in Colorectal Cancer. *Ann Surg* 2020; **272:** 342-51.
103 Tonduangu N, Le Borgne P, Lefebvre F*, et al.* Prognostic Value of C-Reactive Protein to Lymphocyte Ratio (CLR) in Emergency Department Patients with SARS-CoV-2 Infection. *J Pers Med* 2021; **11**.
104 Mayne KJ, Lees JS, Rutherford E*, et al.* Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios: associations with mortality in a haemodialysis cohort. *Clinical kidney journal* 2023; **16:** 512-20.
105 Aikawa T, Takagi H, Ishikawa K, Kuno T. Myocardial injury characterized by elevated cardiac troponin and in-hospital mortality of COVID-19: An insight from a meta-analysis. *J Med Virol* 2020.
106 Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. *JAMA Cardiol* 2020.
107 Kotecha T, Knight DS, Razvi Y*, et al.* Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J* 2021; **42:** 1866-78.
108 Wibowo A, Pranata R, Akbar MR, Purnomowati A, Martha JW. Prognostic performance of troponin in COVID-19: A diagnostic meta-analysis and meta-regression. *Int J Infect Dis* 2021; **105:** 312-8.
109 Solaro RJ, Rarick HM. Troponin and tropomyosin: proteins that switch on and tune in the activity of cardiac myofilaments. *Circ Res* 1998; **83:** 471-80.

110 McCarthy CP, Raber I, Chapman AR, Sandoval Y, Apple FS, Mills NL, Januzzi JL, Jr. Myocardial Injury in the Era of High-Sensitivity Cardiac Troponin Assays: A Practical Approach for Clinicians. *JAMA Cardiol* 2019; **4:** 1034-42.
111 Shah ASV, Anand A, Strachan FE*, et al.* High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *Lancet* 2018; **392:** 919-28.
112 Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: Possible mechanisms. *Life Sci* 2020; **253:** 117723.
113 Nie SF, Yu M, Xie T*, et al.* Cardiac Troponin I Is an Independent Predictor for Mortality in Hospitalized Patients With COVID-19. *Circulation* 2020; **142:** 608-10.
114 Shi S, Qin M, Cai Y*, et al.* Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J* 2020; **41:** 2070-9.
115 Shi S, Qin M, Shen B*, et al.* Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020.
116 Korff S, Katus HA, Giannitsis E. Differential diagnosis of elevated troponins. *Heart* 2006; **92:** 987-93.
117 Hanson PJ, Liu-Fei F, Ng C*, et al.* Characterization of COVID-19-associated cardiac injury: evidence for a multifactorial disease in an autopsy cohort. *Lab Invest* 2022; **102:** 814-25.
118 Imazio M, Klingel K, Kindermann I, Brucato A, De Rosa FG, Adler Y, De Ferrari GM. COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? *Heart* 2020; **106:** 1127-31.
119 Olsson LG, Swedberg K, Cleland JG*, et al.* Prognostic importance of plasma NT-pro BNP in chronic heart failure in patients treated with a beta-blocker: results from the Carvedilol Or Metoprolol European Trial (COMET) trial. *Eur J Heart Fail* 2007; **9:** 795-801.
120 Zinellu A, Sotgia S, Carru C, Mangoni AA. B-Type Natriuretic Peptide Concentrations, COVID-19 Severity, and Mortality: A Systematic Review and Meta-Analysis With Meta-Regression. *Front Cardiovasc Med* 2021; **8:** 690790.
121 O'Donnell C, Ashland MD, Vasti EC*, et al.* N-Terminal Pro-B-Type Natriuretic Peptide as a Biomarker for the Severity and Outcomes With COVID-19 in a Nationwide Hospitalized Cohort. *J Am Heart Assoc* 2021; **10:** e022913.
122 Sorrentino S, Cacia M, Leo I*, et al.* B-Type Natriuretic Peptide as Biomarker of COVID-19 Disease Severity-A Meta-Analysis. *J Clin Med* 2020; **9**.
123 Sheth A, Modi M, Dawson D, Dominic P. Prognostic value of cardiac biomarkers in COVID-19 infection. *Sci Rep* 2021; **11:** 4930.
124 Gao L, Jiang D, Wen XS*, et al.* Prognostic value of NT-proBNP in patients with severe COVID-19. *Respir Res* 2020; **21:** 83.
125 Selcuk M, Keskin M, Cinar T*, et al.* Prognostic significance of N-Terminal Pro-BNP in patients with COVID-19 pneumonia without previous history of heart failure. *European Heart Journal* 2021; **42:** ehab724.0866.
126 Wang L, Chen F, Bai L, Bai L, Huang Z, Peng Y. Association between NT-proBNP Level and the Severity of COVID-19 Pneumonia. *Cardiology Research and Practice* 2021; **2021:** 5537275.
127 Pranata R, Huang I, Lukito AA, Raharjo SB. Elevated N-terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID-19: systematic review and meta-analysis. *Postgraduate Medical Journal* 2020; **96:** 387.
128 Stefanini GG, Chiarito M, Ferrante G*, et al.* Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19. *Heart* 2020; **106:** 1512-8.
129 Barco S, Valerio L, Ageno W*, et al.* Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000-18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database. *Lancet Respir Med* 2021; **9:** 33-42.
130 Kearon C, de Wit K, Parpia S*, et al.* Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. *N Engl J Med* 2019; **381:** 2125-34.
131 Jevnikar M, Sanchez O, Chocron R*, et al.* Prevalence of pulmonary embolism in patients with COVID-19 at the time of hospital admission. *Eur Respir J* 2021; **58**.

132 Klok FA, Kruip M, van der Meer NJM, *et al.* Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res* 2020; **191:** 148-50.
133 Gomez CA, Sun CK, Tsai IT, *et al.* Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: a systematic review and meta-analysis. *Sci Rep* 2021; **11:** 16025.
134 Lopez-Castaneda S, Garcia-Larragoiti N, Cano-Mendez A, *et al.* Inflammatory and Prothrombotic Biomarkers Associated With the Severity of COVID-19 Infection. *Clin Appl Thromb Hemost* 2021; **27:** 1076029621999099.
135 Elberts SJ, Bateman R, Koutsoubis A, London KS, White JL, Fields JM. The impact of COVID-19 on the sensitivity of D-dimer for pulmonary embolism. *Acad Emerg Med* 2021; **28:** 1142-9.
136 Revel MP, Beeker N, Porcher R, *et al.* What level of D-dimers can safely exclude pulmonary embolism in COVID-19 patients presenting to the emergency department? *Eur Radiol* 2022; **32:** 2704-12.
137 Logothetis CN, Weppelmann TA, Jordan A, Hanna C, Zhang S, Charkowick S, Oxner A. D-Dimer Testing for the Exclusion of Pulmonary Embolism Among Hospitalized Patients With COVID-19. *JAMA Netw Open* 2021; **4:** e2128802.
138 Laouan Brem F, Asmae B, Amane Y, *et al.* Diagnostic Accuracy of D-Dimers for Predicting Pulmonary Embolism in COVID-19-Patients. *Clin Appl Thromb Hemost* 2021; **27:** 10760296211057901.
139 Riyahi S, Dev H, Behzadi A, *et al.* Pulmonary Embolism in Hospitalized Patients with COVID-19: A Multicenter Study. *Radiology* 2021; **301:** E426-E33.
140 Khan MZ, Jamal Y, Sutton B, Rauf F. Venous thromboembolism in patients with COVID-19 and correlation with D-dimers: a single-centre experience. *BMJ Open Respir Res* 2020; **7**.
141 Mouhat B, Besutti M, Bouiller K, *et al.* Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients. *Eur Respir J* 2020; **56**.
142 Nadeem I, Anwar A, Jordon L, Mahdi N, Rasool MU, Dakin J, Lok S. Relationship of D-dimer and prediction of pulmonary embolism in hospitalized COVID-19 patients: a multicenter study. *Future Microbiol* 2021; **16:** 863-70.
143 Tuck AA, White HL, Abdalla BA, *et al.* To scan or not to scan – D-dimers and computed tomography pulmonary angiography in the era of COVID-19. *Clinical Medicine* 2021; **21:** e155.
144 Kwee RM, Adams HJA, Kwee TC. Pulmonary embolism in patients with COVID-19 and value of D-dimer assessment: a meta-analysis. *Eur Radiol* 2021; **31:** 8168-86.
145 Ventura-Diaz S, Quintana-Perez JV, Gil-Boronat A, *et al.* A higher D-dimer threshold for predicting pulmonary embolism in patients with COVID-19: a retrospective study. *Emerg Radiol* 2020; **27:** 679-89.
146 Leonard-Lorant I, Delabranche X, Severac F, *et al.* Acute Pulmonary Embolism in Patients with COVID-19 at CT Angiography and Relationship to d-Dimer Levels. *Radiology* 2020; **296:** E189-E91.
147 BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19. *British Thoracic Society* V4.0 31 August 2021.
148 Gustian H, Pratiwi RAB, Riantie R. Comparison of D-Dimer Level on Mild, Moderate and Severe COVID-19 at Immanuel Hospital Bandung City October 1 st - December 31 st, 2020. *Blood* 2021; **138:** 4268-.
149 Conte G, Cei M, Evangelista I, Colombo A, Vitale J, Mazzone A, Mumoli N. The Meaning of D-Dimer value in Covid-19. *Clin Appl Thromb Hemost* 2021; **27:** 10760296211017668.
150 Berger JS, Kunichoff D, Adhikari S, *et al.* Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19. *Arterioscler Thromb Vasc Biol* 2020; **40:** 2539-47.
151 Yao Y, Cao J, Wang Q, *et al.* D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *J Intensive Care* 2020; **8:** 49.
152 Zhan H, Chen H, Liu C, Cheng L, Yan S, Li H, Li Y. Diagnostic Value of D-Dimer in COVID-19: A Meta-Analysis and Meta-Regression. *Clin Appl Thromb Hemost* 2021; **27:** 10760296211010976.

153 He X, Yao F, Chen J*, et al.* The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. *Sci Rep* 2021; **11:** 1830.
154 Poudel A, Poudel Y, Adhikari A*, et al.* D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. *PLoS One* 2021; **16:** e0256744.
155 Hayiroglu MI, Cicek V, Kilic S, Cinar T. Mean serum D-dimer level to predict in-hospital mortality in COVID-19. *Rev Assoc Med Bras (1992)* 2021; **67:** 437-42.
156 Long H, Nie L, Xiang X*, et al.* D-Dimer and Prothrombin Time Are the Significant Indicators of Severe COVID-19 and Poor Prognosis. *Biomed Res Int* 2020; **2020:** 6159720.
157 Simadibrata DM, Lubis AM. D-dimer levels on admission and all-cause mortality risk in COVID-19 patients: a meta-analysis. *Epidemiol Infect* 2020; **148:** e202.
158 Varikasuvu SR, Varshney S, Dutt N, Munikumar M, Asfahan S, Kulkarni PP, Gupta P. D-dimer, disease severity, and deaths (3D-study) in patients with COVID-19: a systematic review and meta-analysis of 100 studies. *Sci Rep* 2021; **11:** 21888.
159 Bashash D, Hosseini-Baharanchi FS, Rezaie-Tavirani M, Safa M, Akbari Dilmaghani N, Faranoush M, Abolghasemi H. The Prognostic Value of Thrombocytopenia in COVID-19 Patients; a Systematic Review and Meta-Analysis. *Arch Acad Emerg Med* 2020; **8:** e75.
160 Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, Shang Y. Thrombocytopenia and its association with mortality in patients with COVID-19. *J Thromb Haemost* 2020; **18:** 1469-72.
161 Jiang SQ, Huang QF, Xie WM, Lv C, Quan XQ. The association between severe COVID-19 and low platelet count: evidence from 31 observational studies involving 7613 participants. *Br J Haematol* 2020; **190:** e29-e33.
162 Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta* 2020; **506:** 145-8.
163 Zhu Y, Zhang J, Li Y, Liu F, Zhou Q, Peng Z. Association between thrombocytopenia and 180-day prognosis of COVID-19 patients in intensive care units: A two-center observational study. *PLoS One* 2021; **16:** e0248671.
164 Guan WJ, Ni ZY, Hu Y*, et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382:** 1708-20.
165 Rampotas A, Pavord S. Platelet aggregates, a marker of severe COVID-19 disease. *J Clin Pathol* 2021; **74:** 750-1.
166 Comer SP, Cullivan S, Szklanna PB*, et al.* COVID-19 induces a hyperactive phenotype in circulating platelets. *PLoS Biol* 2021; **19:** e3001109.
167 Delshad M, Safaroghli-Azar A, Pourbagheri-Sigaroodi A, Poopak B, Shokouhi S, Bashash D. Platelets in the perspective of COVID-19; pathophysiology of thrombocytopenia and its implication as prognostic and therapeutic opportunity. *Int Immunopharmacol* 2021; **99:** 107995-.
168 Gómez-Mesa JE, Galindo-Coral S, Montes MC, Muñoz Martin AJ. Thrombosis and Coagulopathy in COVID-19. *Curr Probl Cardiol* 2021; **46:** 100742.
169 Bao C, Tao X, Cui W, Yi B, Pan T, Young KH, Qian W. SARS-CoV-2 induced thrombocytopenia as an important biomarker significantly correlated with abnormal coagulation function, increased intravascular blood clot risk and mortality in COVID-19 patients. *Exp Hematol Oncol* 2020; **9:** 16.
170 Bomhof G, Mutsaers P, Leebeek FWG, Te Boekhorst PAW, Hofland J, Croles FN, Jansen AJG. COVID-19-associated immune thrombocytopenia. *Br J Haematol* 2020; **190:** e61-e4.
171 Philippe A, Chocron R, Bonnet G*, et al.* Platelet activation and coronavirus disease 2019 mortality: Insights from coagulopathy, antiplatelet therapy and inflammation. *Archives of cardiovascular diseases* 2023.
172 Jolliffe DA, Camargo CA, Jr., Sluyter JD*, et al.* Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised controlled trials. *medRxiv* 2020.
173 Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. *PLoS One* 2020; **15:** e0239252.
174 Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D Deficiency and Treatment with COVID-19 Incidence. *medRxiv* 2020.

175 Liu N, Sun J, Wang X, Zhang T, Zhao M, Li H. Low vitamin D status is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis. *Int J Infect Dis* 2021; **104:** 58-64.
176 Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. *JAMA Netw Open* 2020; **3:** e2019722.
177 Demir M, Demir F, Aygun H. Vitamin D deficiency is associated with COVID-19 positivity and severity of the disease. *J Med Virol* 2021; **93:** 2992-9.
178 Hurst EA, Mellanby RJ, Handel I*, et al.* Vitamin D insufficiency in COVID-19 and influenza A, and critical illness survivors: a cross-sectional study. *BMJ Open* 2021; **11:** e055435.
179 Panagiotou G, Tee SA, Ihsan Y*, et al.* Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalized with COVID-19 are associated with greater disease severity. *Clin Endocrinol (Oxf)* 2020; **93:** 508-11.
180 Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcala Diaz JF, Lopez Miranda J, Bouillon R, Quesada Gomez JM. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". *J Steroid Biochem Mol Biol* 2020; **203:** 105751.
181 Annweiler G, Corvaisier M, Gautier J, Dubee V, Legrand E, Sacco G, Annweiler C. Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study. *Nutrients* 2020; **12**.
182 Alcala-Diaz JF, Limia-Perez L, Gomez-Huelgas R*, et al.* Calcifediol Treatment and Hospital Mortality Due to COVID-19: A Cohort Study. *Nutrients* 2021; **13**.
183 Chen J, Mei K, Xie L*, et al.* Low vitamin D levels do not aggravate COVID-19 risk or death, and vitamin D supplementation does not improve outcomes in hospitalized patients with COVID-19: a meta-analysis and GRADE assessment of cohort studies and RCTs. *Nutrition Journal* 2021; **20:** 89.
184 Murai IH, Fernandes AL, Sales LP*, et al.* Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. *JAMA* 2021; **325:** 1053-60.
185 Ferrari D, Locatelli M. No significant association between vitamin D and COVID-19: A retrospective study from a northern Italian hospital. *Int J Vitam Nutr Res* 2021; **91:** 200-3.
186 Nasiri M, Khodadadi J, Molaei S. Does vitamin D serum level affect prognosis of COVID-19 patients? *Int J Infect Dis* 2021; **107:** 264-7.
187 Chiodini I, Gatti D, Soranna D*, et al.* Vitamin D Status and SARS-CoV-2 Infection and COVID-19 Clinical Outcomes. *Front Public Health* 2021; **9:** 736665.
188 The National Institutes of Health (NIH) COVID-19 Treatment Guidelines. *Downloaded from https://wwwcovid19treatmentguidelinesnihgov/ on 3/17/2022* 21 April 2021.
189 *COVID-19 rapid guideline: managing the long-term effects of COVID-19*. London. 2020.
190 El-Solh AA, Meduri UG, Lawson Y, Carter M, Mergenhagen KA. Clinical Course and Outcome of COVID-19 Acute Respiratory Distress Syndrome: Data From a National Repository. *J Intensive Care Med* 2021; **36:** 664-72.
191 Sokhi J, Khera J, El-Hibri F*, et al.* Non-pulmonary manifestations of coronavirus disease 2019 (COVID-19): case report. *Journal of Emergency and Critical Care Medicine* 2020; **5**.
192 AlSamman M, Caggiula A, Ganguli S, Misak M, Pourmand A. Non-respiratory presentations of COVID-19, a clinical review. *Am J Emerg Med* 2020; **38:** 2444-54.
193 Gupta A, Madhavan MV, Sehgal K*, et al.* Extrapulmonary manifestations of COVID-19. *Nature Medicine* 2020; **26:** 1017-32.
194 Turk C, Turk S, Malkan UY, Haznedaroglu IC. Three critical clinicobiological phases of the human SARS-associated coronavirus infections. *Eur Rev Med Pharmacol Sci* 2020; **24:** 8606-20.
195 Canas LS, Sudre CH, Capdevila Pujol J*, et al.* Early detection of COVID-19 in the UK using self-reported symptoms: a large-scale, prospective, epidemiological surveillance study. *The Lancet Digital Health* 2021; **3:** e587-e98.
196 Dhouib W, Maatoug J, Ayouni I, Zammit N, Ghammem R, Fredj SB, Ghannem H. The incubation period during the pandemic of COVID-19: a systematic review and meta-analysis. *Syst Rev* 2021; **10:** 101.

197 Chen CH, Lin SW, Shen CF, Hsieh KS, Cheng CM. Biomarkers during COVID-19: Mechanisms of Change and Implications for Patient Outcomes. *Diagnostics (Basel)* 2022; **12**.
198 Santa Cruz A, Mendes-Frias A, Oliveira AI*, et al.* Interleukin-6 Is a Biomarker for the Development of Fatal Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia. *Front Immunol* 2021; **12:** 613422.
199 Ouyang SM, Zhu HQ, Xie YN*, et al.* Temporal changes in laboratory markers of survivors and non-survivors of adult inpatients with COVID-19. *BMC Infect Dis* 2020; **20:** 952.
200 Zeng Z, Yu H, Chen H*, et al.* Longitudinal changes of inflammatory parameters and their correlation with disease severity and outcomes in patients with COVID-19 from Wuhan, China. *Crit Care* 2020; **24:** 525.
201 Asghar MS, Haider Kazmi SJ, Khan NA, Akram M, Hassan M, Rasheed U, Ahmed Khan S. Poor Prognostic Biochemical Markers Predicting Fatalities Caused by COVID-19: A Retrospective Observational Study From a Developing Country. *Cureus* 2020; **12:** e9575.
202 Wang Y, Shu H, Liu H*, et al.* The peak levels of highly sensitive troponin I predicts in-hospital mortality in COVID-19 patients with cardiac injury: a retrospective study. *Eur Heart J Acute Cardiovasc Care* 2021; **10:** 6-15.
203 Le Terrier C, Suh N, Wozniak H*, et al.* Delayed intubation is associated with mortality in patients with severe COVID-19: A single-centre observational study in Switzerland. *Anaesth Crit Care Pain Med* 2022; **41:** 101092.
204 Chu DK, Kim LH, Young PJ*, et al.* Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018; **391:** 1693-705.
205 Grieco DL, Menga LS, Cesarano M*, et al.* Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. *Jama* 2021; **325:** 1731-43.
206 Cena T, Cammarota G, Azzolina D*, et al.* Predictors of intubation and mortality in COVID-19 patients: a retrospective study. *Journal of Anesthesia, Analgesia and Critical Care* 2021; **1:** 19.
207 Mejía F, Medina C, Cornejo E*, et al.* Oxygen saturation as a predictor of mortality in hospitalized adult patients with COVID-19 in a public hospital in Lima, Peru. *PLoS One* 2020; **15:** e0244171.
208 Vera M, Kattan E, Born P*, et al.* Intubation timing as determinant of outcome in patients with acute respiratory distress syndrome by SARS-CoV-2 infection. *J Crit Care* 2021; **65:** 164-9.
209 Vest MT, Caplan R, Fawcett M, Deitchman AR, Valentino D, Gajera M, Jurkovitz CT. Intubation Timing in COVID-19 Based on ROX Index and Association With Patient Outcomes. *Respir Care* 2022; **67:** 1291-9.
210 Nozari A, Mukerji S, Vora M*, et al.* Postintubation Decline in Oxygen Saturation Index Predicts Mortality in COVID-19: A Retrospective Pilot Study. *Crit Care Res Pract* 2021; **2021:** 6682944.
211 Chua EX, Wong ZZ, Hasan MS*, et al.* Prone ventilation in intubated COVID-19 patients: a systematic review and meta-analysis. *Braz J Anesthesiol* 2022.
212 O'Carroll O, MacCann R, O'Reilly A*, et al.* Remote monitoring of oxygen saturation in individuals with COVID-19 pneumonia. *Eur Respir J* 2020; **56**.
213 Sartini S, Massobrio L, Cutuli O*, et al.* Role of SatO2, PaO2/FiO2 Ratio and PaO2 to Predict Adverse Outcome in COVID-19: A Retrospective, Cohort Study. *Int J Environ Res Public Health* 2021; **18**.
214 Zinellu A, De Vito A, Scano V*, et al.* The PaO2/FiO2 ratio on admission is independently associated with prolonged hospitalization in COVID-19 patients. *J Infect Dev Ctries* 2021; **15:** 353-9.
215 Downing J, Cardona S, Alfalasi R*, et al.* Predictors of intubation in COVID-19 patients undergoing awake proning in the emergency department. *Am J Emerg Med* 2021; **49:** 276-86.
216 Chen J, Zhu YF, Du ZQ*, et al.* Predictors of mechanical ventilation for COVID-19: combined data from three designated hospitals. *Eur Rev Med Pharmacol Sci* 2020; **24:** 13065-71.
217 Tobin MJ, Jubran A, Laghi F. P (aO(2)) /F (IO(2)) ratio: the mismeasure of oxygenation in COVID-19. *Eur Respir J* 2021; **57**.

218 Tobin MJ, Jubran A, Laghi F. Hypoxaemia does not necessitate tracheal intubation in COVID-19 patients. Comment on Br J Anaesth 2021; 126: 44-7. *Br J Anaesth* 2021; **126:** e75-e6.
219 Kotani T, Shono A. Roles of Electrical Impedance Tomography in Determining a Lung Protective Strategy for Acute Respiratory Distress Syndrome in the Era of Coronavirus Disease 2019. *Jma j* 2021; **4:** 81-5.
220 Tomasino S, Sassanelli R, Marescalco C, Meroi F, Vetrugno L, Bove T. Electrical Impedance Tomography and Prone Position During Ventilation in COVID-19 Pneumonia: Case Reports and a Brief Literature Review. *Semin Cardiothorac Vasc Anesth* 2020; **24:** 287-92.
221 Perier F, Tuffet S, Maraffi T*, et al.* Electrical impedance tomography to titrate positive end-expiratory pressure in COVID-19 acute respiratory distress syndrome. *Crit Care* 2020; **24:** 678.
222 van der Zee P, Somhorst P, Endeman H, Gommers D. Electrical Impedance Tomography for Positive End-Expiratory Pressure Titration in COVID-19-related Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2020; **202:** 280-4.
223 Kapur S, Sweeney MO, Sauer W, MacRae CA. Non-invasive Thoracic Impedance Changes in COVID-19 Pulmonary Infection. *J Cardiovasc Transl Res* 2021; **14:** 387-9.
224 Luepker RV, Michael JR, Warbasse JR. Transthoracic electrical impedance; quantitative evaluation of a non-invasive measure of thoracic fluid volume. *Am Heart J* 1973; **85:** 83-93.
225 Lu Y, Murugiah K, Jones PW*, et al.* Trends in Thoracic Impedance and Arrhythmia Burden Among Patients with Implanted Cardiac Defibrillators During the COVID-19 Pandemic. *medRxiv* 2021.
226 Bangalore S, Sharma A, Slotwiner A*, et al.* ST-Segment Elevation in Patients with Covid-19 - A Case Series. *N Engl J Med* 2020; **382:** 2478-80.
227 Loghin C, Chauhan S, Lawless SM. Pseudo-Acute Myocardial Infarction in a Young COVID-19 Patient. *JACC Case Rep* 2020; **2:** 1284-8.
228 Minhas AS, Scheel P, Garibaldi B*, et al.* Takotsubo Syndrome in the Setting of COVID-19. *JACC Case Rep* 2020; **2:** 1321-5.
229 Doyen D, Moceri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. *Lancet* 2020; **395:** 1516.
230 Capaccione KM, Leb JS, D'Souza B, Utukuri P, Salvatore MM. Acute myocardial infarction secondary to COVID-19 infection: A case report and review of the literature. *Clin Imaging* 2021; **72:** 178-82.
231 Ong E, Castro-Dominguez Y, Brennan J, Oen-Hsiao J. COVID-19 complicated by ST-segment elevation myocardial infarction in a 29-year-old patient. *Catheter Cardiovasc Interv* 2021; **97:** 267-71.
232 Tedeschi D, Rizzi A, Biscaglia S, Tumscitz C. Acute myocardial infarction and large coronary thrombosis in a patient with COVID-19. *Catheter Cardiovasc Interv* 2021; **97:** 272-7.
233 Persson J, Shorofsky M, Leahy R, Friesen R, Khanna A, Cole L, Kim JS. ST-Elevation Myocardial Infarction due to Acute Thrombosis in an Adolescent With COVID-19. *Pediatrics* 2021; **148:** e2020049793.
234 Mehraeen E, Seyed Alinaghi SA, Nowroozi A*, et al.* A systematic review of ECG findings in patients with COVID-19. *Indian Heart J* 2020; **72:** 500-7.
235 Inciardi RM, Lupi L, Zaccone G*, et al.* Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5:** 819-24.
236 Singh S, Desai R, Gandhi Z*, et al.* Takotsubo Syndrome in Patients with COVID-19: a Systematic Review of Published Cases. *SN Compr Clin Med* 2020; **2:** 2102-8.
237 Daniels CJ, Rajpal S, Greenshields JT*, et al.* Prevalence of Clinical and Subclinical Myocarditis in Competitive Athletes With Recent SARS-CoV-2 Infection: Results From the Big Ten COVID-19 Cardiac Registry. *JAMA Cardiol* 2021; **6:** 1078-87.
238 Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. *Cardiovasc Pathol* 2021; **50:** 107300.
239 Shah RM, Shah M, Shah S, Li A, Jauhar S. Takotsubo Syndrome and COVID-19: Associations and Implications. *Curr Probl Cardiol* 2021; **46:** 100763.
240 Musikantow DR, Turagam MK, Sartori S*, et al.* Atrial Fibrillation in Patients Hospitalized With COVID-19: Incidence, Predictors, Outcomes, and Comparison to Influenza. *JACC Clin Electrophysiol* 2021; **7:** 1120-30.

241 Li Z, Shao W, Zhang J*, et al.* Prevalence of Atrial Fibrillation and Associated Mortality Among Hospitalized Patients With COVID-19: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med* 2021; **8:** 720129.
242 Denegri A, Sola M, Morelli M*, et al.* Arrhythmias in COVID-19/SARS-CoV-2 Pneumonia Infection: Prevalence and Implication for Outcomes. *J Clin Med* 2022; **11**.
243 Eneizat Mahdawi T, Wang H, Haddadin FI, Al-Qaysi D, Wylie JV. Heart block in patients with coronavirus disease 2019: A case series of 3 patients infected with SARS-CoV-2. *HeartRhythm Case Rep* 2020; **6:** 652-6.
244 Dagher L, Wanna B, Mikdadi G, Young M, Sohns C, Marrouche NF. High-degree atrioventricular block in COVID-19 hospitalized patients. *Europace* 2021; **23:** 451-5.
245 Bhasin V, Carrillo M, Ghosh B, Moin D, Maglione TJ, Kassotis J. Reversible complete heart block in a patient with coronavirus disease 2019. *Pacing Clin Electrophysiol* 2021; **44:** 1939-43.
246 Chen JH, Robinson B, Patel P, Kata P, Kanukuntla AK, Okere A, Cheriyath P. Transient Complete Heart Block in a Patient With COVID-19. *Cureus* 2021; **13:** e15796.
247 Azarkish M, Laleh Far V, Eslami M, Mollazadeh R. Transient complete heart block in a patient with critical COVID-19. *Eur Heart J* 2020; **41:** 2131.
248 Dehghani Firouzabadi M, Goudarzi S, Dehghani Firouzabadi F, Moosaie F. Complete heart block and itchy rash in a patient with COVID-19. *Caspian J Intern Med* 2020; **11:** 569-71.
249 Haddadin FI, Mahdawi TE, Hattar L, Beydoun H, Fram F, Homoud M. A case of complete heart block in a COVID-19 infected patient. *J Cardiol Cases* 2021; **23:** 27-30.
250 Shao F, Xu S, Ma X*, et al.* In-hospital cardiac arrest outcomes among patients with COVID-19 pneumonia in Wuhan, China. *Resuscitation* 2020; **151:** 18-23.
251 Nadkarni VM, Larkin GL, Peberdy MA*, et al.* First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA* 2006; **295:** 50-7.
252 Acharya P, Ranka S, Sethi P*, et al.* Incidence, Predictors, and Outcomes of In-Hospital Cardiac Arrest in COVID-19 Patients Admitted to Intensive and Non-Intensive Care Units: Insights From the AHA COVID-19 CVD Registry. *J Am Heart Assoc* 2021; **10:** e021204.
253 Kochav SM, Coromilas E, Nalbandian A*, et al.* Cardiac Arrhythmias in COVID-19 Infection. *Circ Arrhythm Electrophysiol* 2020; **13:** e008719.
254 Mitacchione G, Schiavone M, Gasperetti A, Forleo GB. Ventricular tachycardia storm management in a COVID-19 patient: a case report. *Eur Heart J Case Rep* 2020; **4:** 1-6.
255 Mukhopadhyay S, Uppal A, Yusuf J, Muheeb G, Agarwal R. COVID-19 induced ventricular tachycardia storm unmasking a clinically silent cardiomyopathy: a case report. *Eur Heart J Case Rep* 2021; **5:** ytab220.
256 Kumar D, Malviya A, Saha A, Roy R, Khan S, Mishra A, Chakraborty R. Ventricular fibrillation storm in COVID 19 responding to steroid therapy: A case report. *IHJ Cardiovascular Case Reports (CVCR)* 2021; **5:** 177-80.
257 Doodnauth AV, Goel R, Chen L, Uppin V, Malik ZR, Patel KH, McFarlane SI. Electrical Storm With Incessant Ventricular Tachycardia in a COVID-19 Patient: Review of Current Evidence. *Cureus* 2021; **13:** e15604.
258 Cho JH, Namazi A, Shelton R*, et al.* Cardiac arrhythmias in hospitalized patients with COVID-19: A prospective observational study in the western United States. *PLoS One* 2020; **15:** e0244533.
259 Dewland TA, Whitman IR, Win S*, et al.* Prospective arrhythmia surveillance after a COVID-19 diagnosis. *Open Heart* 2022; **9**.
260 Diaz-Arocutipa C, Branez-Condorena A, Hernandez AV. QTc prolongation in COVID-19 patients treated with hydroxychloroquine, chloroquine, azithromycin, or lopinavir/ritonavir: A systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf* 2021; **30:** 694-706.
261 Moey MYY, Sengodan PM, Shah N*, et al.* Electrocardiographic Changes and Arrhythmias in Hospitalized Patients With COVID-19. *Circ Arrhythm Electrophysiol* 2020; **13:** e009023.
262 Thakore A, Nguyen J, Pollack S*, et al.* Electrocardiographic manifestations of COVID-19: Effect on cardiac activation and repolarization. *EClinicalMedicine* 2021; **39:** 101057.
263 Garmendia-Prieto B, Carrillo-Garcia P, Gomez-Pavon J. QT interval prolongation in geriatric patients treated for SARS-COV-2 infection: OCTA-COVID study. *Med Clin (Engl Ed)* 2021; **157:** e302-e3.

264 Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004; **350:** 1013-22.
265 Gadaleta F, Llois S, Kaski JC. Corrected QT interval: a prognostic marker in patients with non-ST-segment elevation acute coronary syndrome? *Trends Cardiovasc Med* 2011; **21:** 129-35.
266 Gadaleta FL, Llois SC, Lapuente AR, Batchvarov VN, Kaski JC. Prognostic value of corrected QT-interval prolongation in patients with unstable angina pectoris. *Am J Cardiol* 2003; **92:** 203-5.
267 Bijl M, Verheugt FW. Extreme QT prolongation solely due to reversible myocardial ischemia in single-vessel coronary disease. *Am Heart J* 1992; **123:** 524-6.
268 Yuan M, Zathar Z, Nihaj F, *et al.* ECG changes in hospitalised patients with COVID-19 infection. *Br J Cardiol*; **2021;28:55**.
269 Bergamaschi L, D'Angelo EC, Paolisso P, *et al.* The value of ECG changes in risk stratification of COVID-19 patients. *Ann Noninvasive Electrocardiol* 2021; **26:** e12815.
270 De Carvalho H, Leonard-Pons L, Segard J, *et al.* Electrocardiographic abnormalities in COVID-19 patients visiting the emergency department: a multicenter retrospective study. *BMC Emerg Med* 2021; **21:** 141.
271 Fischer K, Marggraf M, Stark AW, *et al.* Association of ECG parameters with late gadolinium enhancement and outcome in patients with clinical suspicion of acute or subacute myocarditis referred for CMR imaging. *PLoS One* 2020; **15:** e0227134.
272 Lampert J, Miller M, Halperin JL, *et al.* Prognostic Value of Electrocardiographic QRS Diminution in Patients Hospitalized With COVID-19 or Influenza. *Am J Cardiol* 2021; **159:** 129-37.
273 Pepe M, Napoli G, Brindicci G, *et al.* Prognostic value of 12-leads admission electrocardiogram in low-risk patients hospitalized for Covid-19. *Minerva Med* 2021.
274 Mol MBA, Strous MTA, van Osch FHM, *et al.* Heart-rate-variability (HRV), predicts outcomes in COVID-19. *PLOS ONE* 2021; **16:** e0258841.
275 Pinto-Filho MM, Paixão GM, Gomes PR, *et al.* Electrocardiographic findings and prognostic values in patients hospitalised with COVID-19 in the World Heart Federation Global Study. *Heart* 2022.
276 Mele M, Tricarico L, Vitale E, *et al.* Electrocardiographic findings and mortality in covid-19 patients hospitalized in different clinical settings. *Heart Lung* 2022; **53:** 99-103.
277 Tsakok M, Shaw R, Murchison A, *et al.* Diagnostic accuracy of initial chest radiograph compared to SARS-CoV-2 PCR in patients with suspected COVID-19. *BJR Open* 2020; **2:** 20200034.
278 Use of chest imaging in COVID-19: a rapid advice guide. Geneva: World Health Organization; 2020 (WHO/2019-nCoV/Clinical/Radiology_imaging/2020.1). Licence: CC BY-NC-SA 3.0 IGO.
279 Sadiq Z, Rana S, Mahfoud Z, Raoof A. Systematic review and meta-analysis of chest radiograph (CXR) findings in COVID-19. *Clin Imaging* 2021; **80:** 229-38.
280 Rousan LA, Elobeid E, Karrar M, Khader Y. Chest x-ray findings and temporal lung changes in patients with COVID-19 pneumonia. *BMC Pulmonary Medicine* 2020; **20:** 245.
281 Masood L, Zafar SB, Wahla MS, Gul S, Akhtar S, Rana AI. Progression and Resolution of COVID-19 Pneumonia on Chest Radiograph. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP* 2021; **31:** 258-61.
282 Abdelnour LH, Abdalla ME. Progression of CXR features on a COVID-19 survivor. *IDCases* 2020; **21:** e00834.
283 Mason SE, Dieffenbach PB, Englert JA, *et al.* Semi-quantitative visual assessment of chest radiography is associated with clinical outcomes in critically ill patients. *Respir Res* 2019; **20:** 218.
284 Warren MA, Zhao Z, Koyama T, *et al.* Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. *Thorax* 2018; **73:** 840-6.
285 Monaco CG, Zaottini F, Schiaffino S, *et al.* Chest x-ray severity score in COVID-19 patients on emergency department admission: a two-centre study. *Eur Radiol Exp* 2020; **4:** 68.
286 Au-Yong I, Higashi Y, Giannotti E, *et al.* Chest Radiograph Scoring Alone or Combined with Other Risk Scores for Predicting Outcomes in COVID-19. *Radiology* 2022; **302:** 460-9.
287 Borghesi A, Maroldi R. COVID-19 outbreak in Italy: experimental chest X-ray scoring system for quantifying and monitoring disease progression. *Radiol Med* 2020; **125:** 509-13.

288 Borghesi A, Zigliani A, Golemi S, Carapella N, Maculotti P, Farina D, Maroldi R. Chest X-ray severity index as a predictor of in-hospital mortality in coronavirus disease 2019: A study of 302 patients from Italy. *Int J Infect Dis* 2020; **96:** 291-3.
289 Singh A, Lim YH, Annamalaisamy R, Koteyar SS, Chandran S, Kanodia AK, Khanna N. Chest x-ray scoring as a predictor of COVID-19 disease; correlation with comorbidities and in-hospital mortality. *Scott Med J* 2021; **66:** 101-7.
290 Adarve Castro A, Diaz Antonio T, Cuartero Martinez E, Garcia Gallardo MM, Berma Gascon ML, Dominguez Pinos D. Usefulness of chest X-rays for evaluating prognosis in patients with COVID-19. *Radiologia (Engl Ed)* 2021; **63:** 476-83.
291 Sargent W, Ali S, Kukran S, Harvie M, Soin S. The prognostic value of chest X-ray in patients with COVID-19 on admission and when starting CPAP. *Clin Med (Lond)* 2021; **21:** e14-e9.
292 Valk CMA, Zimatore C, Mazzinari G*, et al.* The Prognostic Capacity of the Radiographic Assessment for Lung Edema Score in Patients With COVID-19 Acute Respiratory Distress Syndrome-An International Multicenter Observational Study. *Front Med (Lausanne)* 2021; **8:** 772056.
293 Maroldi R, Rondi P, Agazzi GM, Ravanelli M, Borghesi A, Farina D. Which role for chest x-ray score in predicting the outcome in COVID-19 pneumonia? *Eur Radiol* 2021; **31:** 4016-22.
294 Li MD, Arun NT, Gidwani M*, et al.* Automated Assessment and Tracking of COVID-19 Pulmonary Disease Severity on Chest Radiographs using Convolutional Siamese Neural Networks. *Radiol Artif Intell* 2020; **2:** e200079.
295 Jiao Z, Choi JW, Halsey K*, et al.* Prognostication of patients with COVID-19 using artificial intelligence based on chest x-rays and clinical data: a retrospective study. *Lancet Digit Health* 2021; **3:** e286-e94.
296 Sun J, Peng L, Li T*, et al.* A Prospective Observational Study to Investigate Performance of a Chest X-ray Artificial Intelligence Diagnostic Support Tool Across 12 U.S. Hospitals. *ArXiv* 2021.
297 Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. *AJR Am J Roentgenol* 2020; **215:** 87-93.
298 Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, Ji W. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* 2020; **296:** E115-E7.
299 Ai T, Yang Z, Hou H*, et al.* Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020; **296:** E32-E40.
300 Chua F, Armstrong-James D, Desai SR*, et al.* The role of CT in case ascertainment and management of COVID-19 pneumonia in the UK: insights from high-incidence regions. *Lancet Respir Med* 2020; **8:** 438-40.
301 Lee CH. The crazy-paving sign. *Radiology* 2007; **243:** 905-6.
302 Kazemi MA, Ghanaati H, Moradi B*, et al.* Prognostic factors of chest CT findings for ICU admission and mortality in patients with COVID-19 pneumonia. *medRxiv* 2020**:** 2020.10.30.20223024.
303 Jin C, Tian C, Wang Y*, et al.* A Pattern Categorization of CT Findings to Predict Outcome of COVID-19 Pneumonia. *Front Public Health* 2020; **8:** 567672.
304 Liu S, Nie C, Xu Q, Xie H, Wang M, Yu C, Hou X. Prognostic value of initial chest CT findings for clinical outcomes in patients with COVID-19. *Int J Med Sci* 2021; **18:** 270-5.
305 Tabatabaei SMH, Talari H, Moghaddas F, Rajebi H. CT Features and Short-term Prognosis of COVID-19 Pneumonia: A Single-Center Study from Kashan, Iran. *Radiol Cardiothorac Imaging* 2020; **2:** e200130.
306 Lei Q, Li G, Ma X*, et al.* Correlation between CT findings and outcomes in 46 patients with coronavirus disease 2019. *Scientific Reports* 2021; **11:** 1103.
307 Okoye C, Finamore P, Bellelli G*, et al.* Computed tomography findings and prognosis in older COVID-19 patients. *BMC Geriatrics* 2022; **22:** 166.
308 Zhou X, Pu Y, Zhang D, Xia Y, Guan Y, Liu S, Fan L. CT findings and dynamic imaging changes of COVID-19 in 2908 patients: a systematic review and meta-analysis. *Acta Radiologica* 2022; **63:** 291-310.
309 Wang Y, Dong C, Hu Y*, et al.* Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology* 2020; **296:** E55-e64.

310 Liu X, Zhou H, Zhou Y*, et al.* Temporal radiographic changes in COVID-19 patients: relationship to disease severity and viral clearance. *Sci Rep* 2020; **10:** 10263.
311 Pan F, Ye T, Sun P*, et al.* Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology* 2020; **295:** 715-21.
312 Esposito A, Palmisano A, Toselli M*, et al.* Chest CT-derived pulmonary artery enlargement at the admission predicts overall survival in COVID-19 patients: insight from 1461 consecutive patients in Italy. *Eur Radiol* 2021; **31:** 4031-41.
313 Ferrante G, Fazzari F, Cozzi O*, et al.* Risk factors for myocardial injury and death in patients with COVID-19: insights from a cohort study with chest computed tomography. *Cardiovasc Res* 2020.
314 Hu Q, Guan H, Sun Z*, et al.* Early CT features and temporal lung changes in COVID-19 pneumonia in Wuhan, China. *European journal of radiology* 2020; **128:** 109017.
315 Planek MIC, Ruge M, Du Fay de Lavallaz JM*, et al.* Cardiovascular findings on chest computed tomography associated with COVID-19 adverse clinical outcomes. *American heart journal plus : cardiology research and practice* 2021; **11:** 100052.
316 Dillinger JG, Benmessaoud FA, Pezel T*, et al.* Coronary Artery Calcification and Complications in Patients With COVID-19. *JACC Cardiovasc Imaging* 2020; **13:** 2468-70.
317 Cereda A, Toselli M, Palmisano A*, et al.* Coronary calcium score as a predictor of outcomes in the hypertensive Covid-19 population: results from the Italian (S) Core-Covid-19 Registry. *Hypertension research : official journal of the Japanese Society of Hypertension* 2022; **45:** 333-43.
318 Lee KK, Rahimi O, Lee CK, Shafi A, Hawwass D. A Meta-Analysis: Coronary Artery Calcium Score and COVID-19 Prognosis. *Medical sciences (Basel, Switzerland)* 2022; **10**.
319 Luchian ML, Lochy S, Motoc A*, et al.* Prognostic Value of Coronary Artery Calcium Score in Hospitalized COVID-19 Patients. *Front Cardiovasc Med* 2021; **8:** 684528.
320 Cosyns B, Motoc A, Luchian ML, Lochy S, Belsack D. Coronary Calcium Score in COVID-19 Hospitalized Patients. *JACC Cardiovasc Imaging* 2020; **13:** 2698.
321 Giannini F, Toselli M, Palmisano A*, et al.* Coronary and total thoracic calcium scores predict mortality and provides pathophysiologic insights in COVID-19 patients. *J Cardiovasc Comput Tomogr* 2021; **15:** 421-30.
322 Ramandi A, Akbarzadeh MA, Khaheshi I, Khalilian MR. Aortic dissection and Covid-19; a comprehensive systematic review. *Curr Probl Cardiol* 2022**:** 101129.
323 Singh V, Choi AD, Leipsic J*, et al.* Use of cardiac CT amidst the COVID-19 pandemic and beyond: North American perspective. *J Cardiovasc Comput Tomogr* 2021; **15:** 16-26.
324 Ji L, Cao C, Gao Y*, et al.* Prognostic value of bedside lung ultrasound score in patients with COVID-19. *Crit Care* 2020; **24:** 700.
325 Lichter Y, Topilsky Y, Taieb P*, et al.* Lung ultrasound predicts clinical course and outcomes in COVID-19 patients. *Intensive Care Med* 2020; **46:** 1873-83.
326 Peng QY, Wang XT, Zhang LN. Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. *Intensive Care Med* 2020; **46:** 849-50.
327 Tan G, Lian X, Zhu Z*, et al.* Use of Lung Ultrasound to Differentiate Coronavirus Disease 2019 (COVID-19) Pneumonia From Community-Acquired Pneumonia. *Ultrasound Med Biol* 2020; **46:** 2651-8.
328 Yasukawa K, Minami T. Point-of-Care Lung Ultrasound Findings in Patients with COVID-19 Pneumonia. *Am J Trop Med Hyg* 2020; **102:** 1198-202.
329 Yasukawa K, Minami T, Boulware DR, Shimada A, Fischer EA. Point-of-Care Lung Ultrasound for COVID-19: Findings and Prognostic Implications From 105 Consecutive Patients. *J Intensive Care Med* 2021; **36:** 334-42.
330 Husain LF, Hagopian L, Wayman D, Baker WE, Carmody KA. Sonographic diagnosis of pneumothorax. *J Emerg Trauma Shock* 2012; **5:** 76-81.
331 Omer T, Cousins C, Lynch T, Le NN, Sajed D, Mailhot T. Lung Ultrasound Findings in COVID-19: A Descriptive Retrospective Study. *Cureus* 2022; **14:** e23375.
332 Volpicelli G, Lamorte A, Villén T. What's new in lung ultrasound during the COVID-19 pandemic. *Intensive Care Med* 2020; **46:** 1445-8.
333 Dweck MR, Bularga A, Hahn RT*, et al.* Global evaluation of echocardiography in patients with COVID-19. *Eur Heart J Cardiovasc Imaging* 2020; **21:** 949-58.

334 Jain SS, Liu Q, Raikhelkar J*, et al.* Indications for and Findings on Transthoracic Echocardiography in COVID-19. *J Am Soc Echocardiogr* 2020; **33:** 1278-84.
335 Ceriani E, Marceca A, Lanfranchi A*, et al.* Early echocardiographic findings in patients hospitalized for COVID-19 pneumonia: a prospective, single center study. *Intern Emerg Med* 2021; **16:** 2173-80.
336 Churchill TW, Bertrand PB, Bernard S*, et al.* Echocardiographic Features of COVID-19 Illness and Association with Cardiac Biomarkers. *J Am Soc Echocardiogr* 2020; **33:** 1053-4.
337 Sud K, Vogel B, Bohra C*, et al.* Echocardiographic Findings in Patients with COVID-19 with Significant Myocardial Injury. *J Am Soc Echocardiogr* 2020; **33:** 1054-5.
338 van den Heuvel FMA, Vos JL, Koop Y*, et al.* Cardiac function in relation to myocardial injury in hospitalised patients with COVID-19. *Neth Heart J* 2020; **28:** 410-7.
339 Rath D, Petersen-Uribe A, Avdiu A*, et al.* Impaired cardiac function is associated with mortality in patients with acute COVID-19 infection. *Clin Res Cardiol* 2020; **109:** 1491-9.
340 Carrizales-Sepulveda EF, Vera-Pineda R, Flores-Ramirez R, Hernandez-Guajardo DA, Perez-Contreras E, Lozano-Ibarra MM, Ordaz-Farias A. Echocardiographic Manifestations in COVID-19: A Review. *Heart Lung Circ* 2021; **30:** 1117-29.
341 Huang S, Vignon P, Mekontso-Dessap A*, et al.* Echocardiography findings in COVID-19 patients admitted to intensive care units: a multi-national observational study (the ECHO-COVID study). *Intensive Care Med* 2022.
342 Zwaenepoel B, Dhont S, Hoste E, Gevaert S, Schaubroeck H. The Prognostic Value of Cardiac Biomarkers and Echocardiography in Critical COVID-19. *Front Cardiovasc Med* 2021; **8:** 752237.
343 Han Y, Chen T, Bryant J*, et al.* Society for Cardiovascular Magnetic Resonance (SCMR) guidance for the practice of cardiovascular magnetic resonance during the COVID-19 pandemic. *J Cardiovasc Magn Reson* 2020; **22:** 26.
344 Kelle S, Bucciarelli-Ducci C, Judd RM*, et al.* Society for Cardiovascular Magnetic Resonance (SCMR) recommended CMR protocols for scanning patients with active or convalescent phase COVID-19 infection. *J Cardiovasc Magn Reson* 2020; **22:** 61.
345 Huang L, Zhao P, Tang D*, et al.* Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. *JACC Cardiovasc Imaging* 2020; **13:** 2330-9.
346 Puntmann VO, Carerj ML, Wieters I*, et al.* Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5:** 1265-73.
347 Li X, Wang H, Zhao R*, et al.* Elevated Extracellular Volume Fraction and Reduced Global Longitudinal Strains in Participants Recovered from COVID-19 without Clinical Cardiac Findings. *Radiology* 2021; **299:** E230-E40.
348 Wang H, Li R, Zhou Z*, et al.* Cardiac involvement in COVID-19 patients: mid-term follow up by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2021; **23:** 14.
349 Drakos S, Chatzantonis G, Bietenbeck M*, et al.* A cardiovascular magnetic resonance imaging-based pilot study to assess coronary microvascular disease in COVID-19 patients. *Sci Rep* 2021; **11:** 15667.
350 Nyberg T, Ferguson NM, Nash SG*, et al.* Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *The Lancet* 2022.
351 Thiruvengadam R, Binayke A, Awasthi A. SARS-CoV-2 delta variant: a persistent threat to the effectiveness of vaccines. *Lancet Infect Dis* 2022; **22:** 301-2.
352 Lauring AS, Tenforde MW, Chappell JD*, et al.* Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *BMJ* 2022; **376:** e069761.
353 Bar-Zeev N, Inglesby T. COVID-19 vaccines: early success and remaining challenges. *Lancet* 2020; **396:** 868-9.
354 Dyer O. Covid-19: Unvaccinated face 11 times risk of death from delta variant, CDC data show. *BMJ* 2021; **374:** n2282.
355 Alfano V, Ercolano S. The Efficacy of Lockdown Against COVID-19: A Cross-Country Panel Analysis. *Appl Health Econ Health Policy* 2020; **18:** 509-17.

356 Rubina K, Shmakova A, Shabanov A*, et al.* Novel prognostic determinants of COVID-19-related mortality: A pilot study on severely-ill patients in Russia. *PLoS One* 2022; **17:** e0264072.
357 D'Rozario R, Raychaudhuri D, Bandopadhyay P*, et al.* Circulating Interleukin-8 Dynamics Parallels Disease Course and Is Linked to Clinical Outcomes in Severe COVID-19. *Viruses* 2023; **15**.
358 Gravrand V, Mellot F, Ackermann F*, et al.* Stratification of COVID-19 Severity Using SeptiCyte RAPID, a Novel Host Immune Response Test. *Viruses* 2023; **15**.
359 Group RC, Horby P, Lim WS*, et al.* Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384:** 693-704.
360 Beigel JH, Tomashek KM, Dodd LE*, et al.* Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; **383:** 1813-26.
361 Jayk Bernal A, Gomes da Silva MM, Musungaie DB*, et al.* Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med* 2022; **386:** 509-20.
362 Hammond J, Leister-Tebbe H, Gardner A*, et al.* Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *N Engl J Med* 2022; **386:** 1397-408.
363 Yoo SM, Liu TC, Motwani Y*, et al.* Factors Associated with Post-Acute Sequelae of SARS-CoV-2 (PASC) After Diagnosis of Symptomatic COVID-19 in the Inpatient and Outpatient Setting in a Diverse Cohort. *Journal of General Internal Medicine* 2022; **37:** 1988-95.
364 Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. *BMJ* 2021; **374:** n1648.
365 Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. *The Lancet* 2022; **399:** 2263-4.
366 Antonelli M, Penfold RS, Merino J*, et al.* Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis* 2022; **22:** 43-55.
367 Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. *Nature Medicine* 2022; **28:** 1461-7.
368 Poudel AN, Zhu S, Cooper N*, et al.* Impact of Covid-19 on health-related quality of life of patients: A structured review. *PLoS One* 2021; **16:** e0259164.
369 Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, Banerjee A. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ* 2021; **372:** n693.

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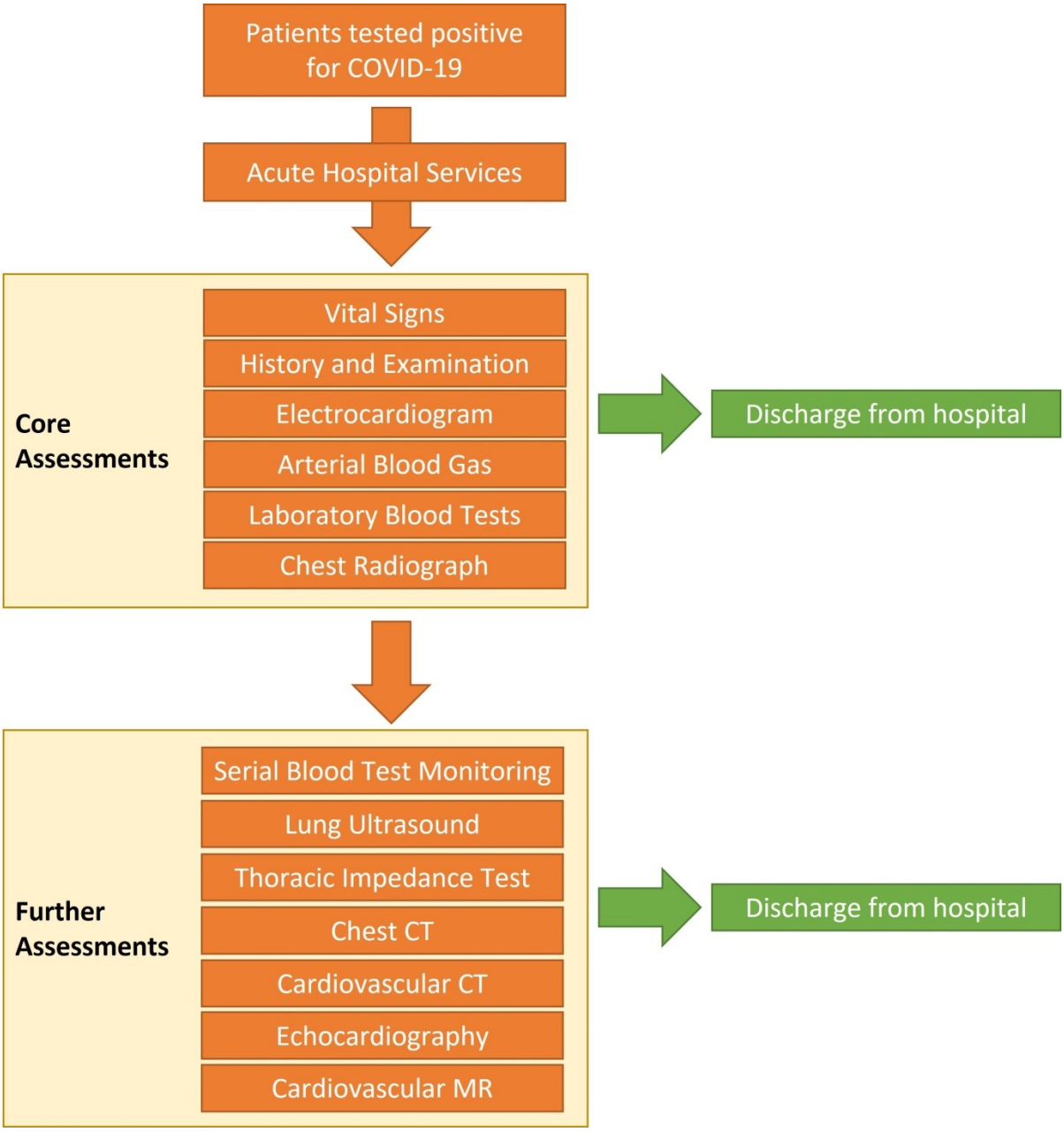

Figure legends

Figure 1: Possible frontline assessment cascade in acute coronavirus disease 19 (COVID-19). Acute COVID-19 patients presenting to acute hospital services may undergo a range of core and further assessments depending on the clinical circumstances. Patients may be admitted to hospital or discharged at any stage along their journeys. CT: computed tomography; MR: magnetic resonance.

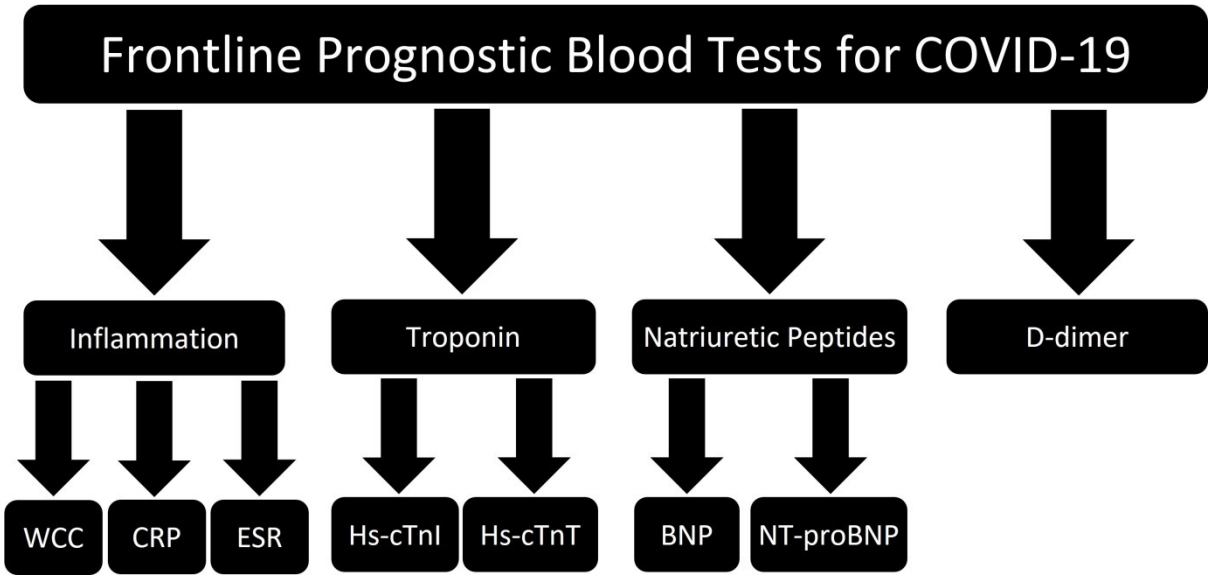

Figure 2: Summary of common blood tests commonly performed on the frontline in coronavirus disease 19 (COVID-19) patients. BNP: B-type natriuretic peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hs-cTnI: high sensitivity cardiac troponin I; Hs-cTnT: high sensitivity cardiac troponin T; NT-proBNP: N-terminal pro-B-type natriuretic peptides; WCC: white cell count.

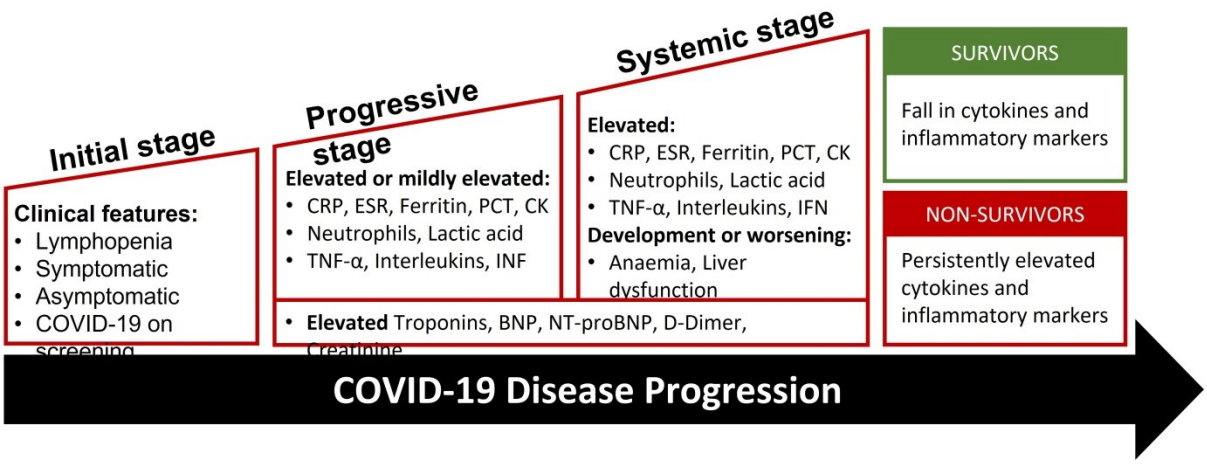

Figure 3: Summary of dynamic biomarker changes in different stages of coronavirus disease 19 (COVID-19) disease progression. BNP: B-type natriuretic peptide; CK: creatine kinase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; INF: interferons; NT-proBNP: N-terminal pro-B-type natriuretic peptides; PCT: procalcitonin; TNF-α: tumour necrosis factor α.

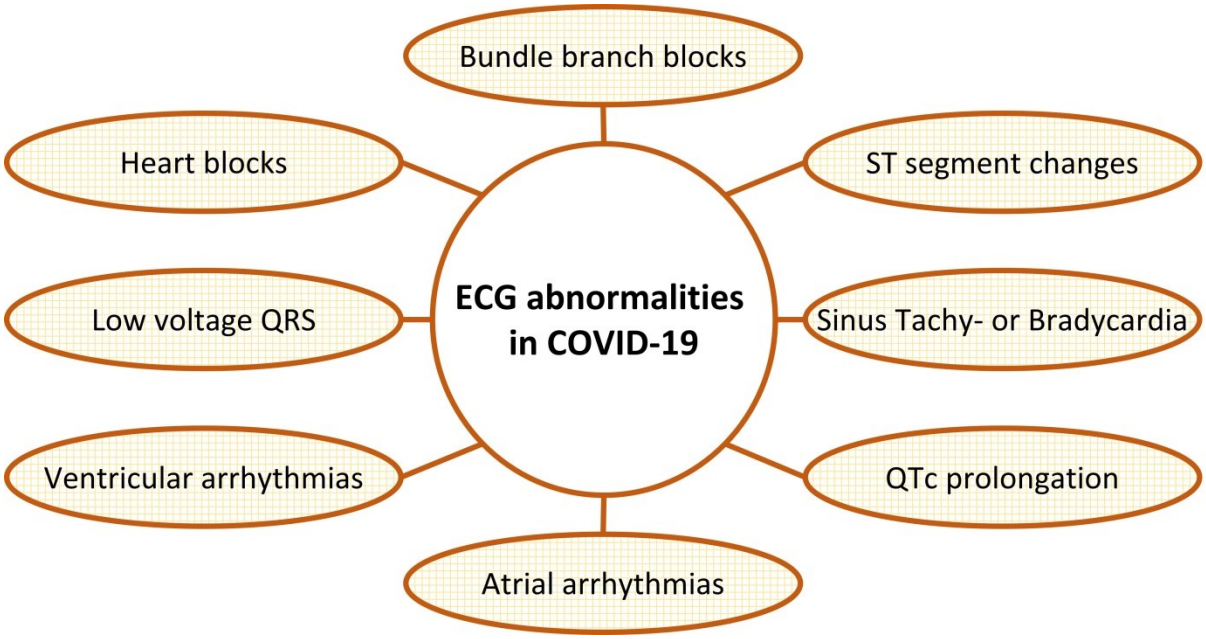

Figure 4: Summary of documented abnormalities on electrocardiogram (ECG) linked to prognosis in coronavirus disease 19 (COVID-19). QTc: corrected QT interval on ECG.

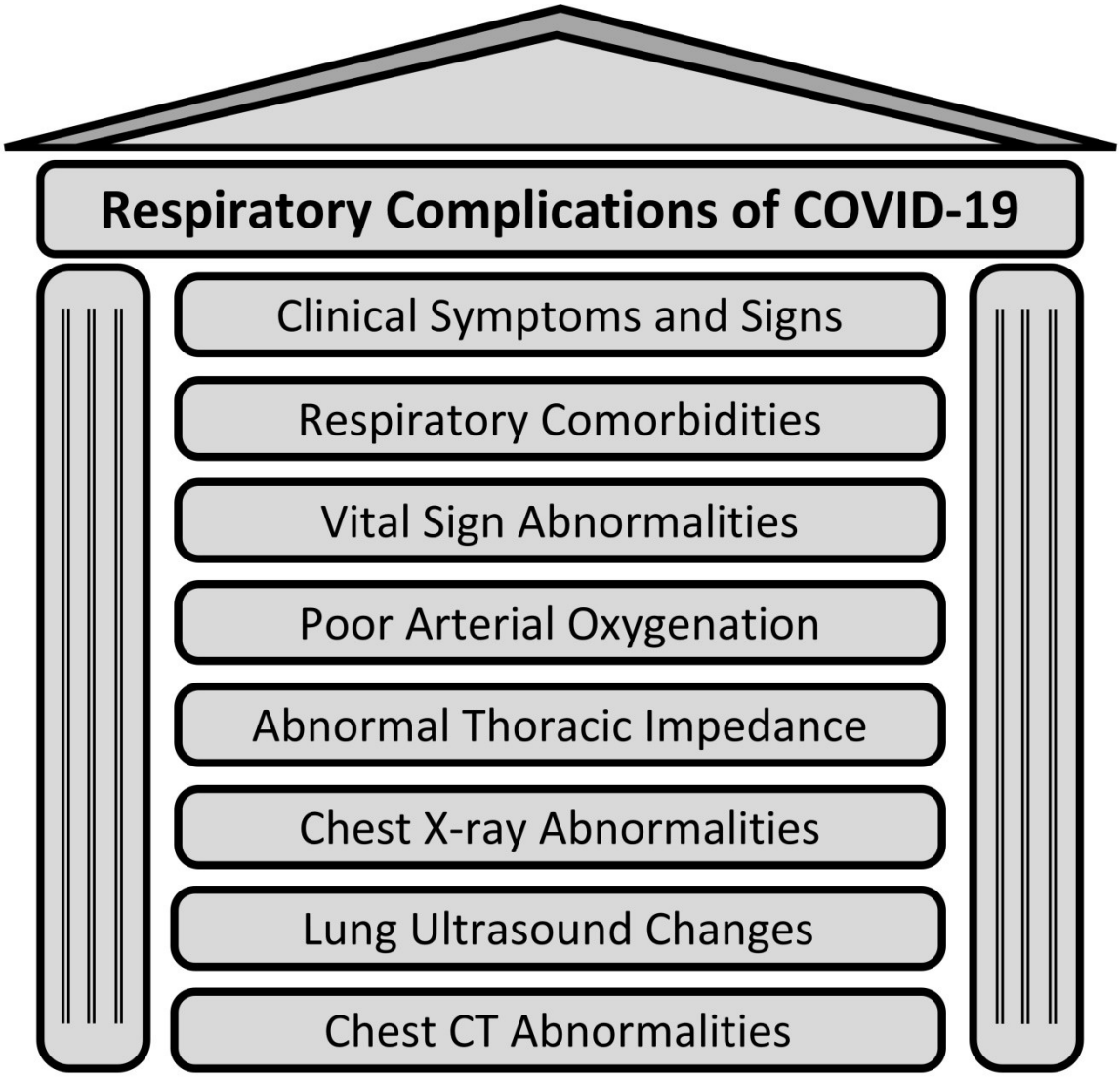

Figure 5: Biomarker assessment of respiratory complications related to coronavirus disease 19 (COVID-19). CT: computed tomography.

Figure 6: Potential usefulness of clinical assessment and biomarkers at each stage of the acute coronavirus disease 19 (COVID-19) infection. Acute COVID-19 can be broadly divided into three (initial, progressive and systemic) stages. Temporal changes in relation to COVID-19 progression is known for certain modes of assessment such as clinical history, examination, vital signs, arterial oxygenation, electrocardiogram, serum biomarkers, CXR, chest CT and lung ultrasound. These markers are potentially effective in the progressive and systemic stages but may be less useful in the initial stage of infection when patients can be asymptomatic without clearcut biomarker abnormalities. Echocardiography may also be useful in the latter stages. Comorbidities are non-modifiable and relevant considerations in all stages. CT: computed tomography; CXR: Chest X-ray.