

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

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In acute coronavirus disease 19 (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, whereas risk scores such as the 4C-score enable multifactorial 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 the bedside assessment of prognostic abnormalities in COVID-19. Chest radiograph (CXR) and computed tomography

(CT) can inform about prognostic pulmonary pathologies, whereas cardiovascular CT detects high-risk features such as coronary artery and aortic calcification. Dynamic changes in biomarkers, such as blood tests, CXR, CT and electrocardiogram 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. First, the pathophysiological basis on which these markers can foretell prognosis in COVID-19 remains poorly understood. Second, certain under-explored tests such as thoracic impedance assessment and cardiovascular magnetic resonance imaging deserve further investigation. Lastly, the prognostic values of most biomarkers in COVID-19 are derived from retrospective analyses. Prospective 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 hospitalized 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 hospitalization 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]. Although 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 randomized trial showed that the discontinuation of ACE inhibitors or ARBs did not significantly affect prognosis [38]. Disorders of lipid metabolism are also prevalent, but their association with adverse outcomes in COVID-19 is weak [32]. Further, although 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 comorbidities, worse respiratory disease exacerbations provoked by COVID-19 [40–45] or both. Further investigation is needed to better answer this question.

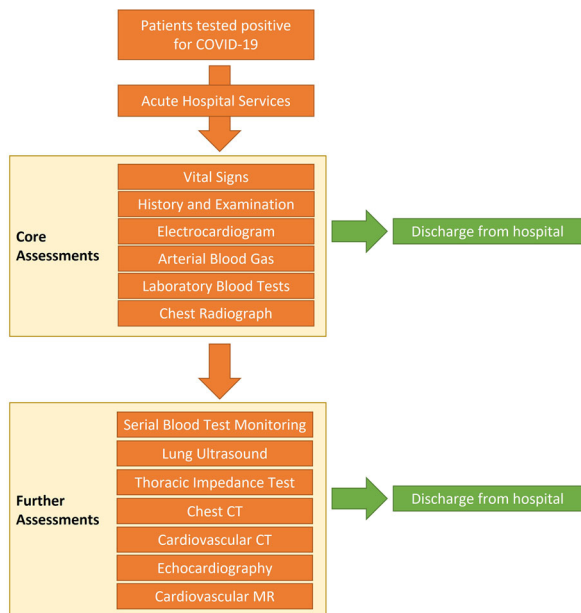
Bacterial coinfection is also linked to a worse prognosis in COVID-19 patients [46]. However, the prevalence of bacterial infection in COVID-19 is considered low [47], and existing evidence does not support the routine use of antibiotics in this setting [48]. There is currently no specific guidance on 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, 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], because 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 (Fig. 1).



**Fig. 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.

### 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 confers a particularly poor prognosis [58]. These observations are unsurprising given that abnormal vital signs are well recognized 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]. First, 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]. Second, 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]. Third, 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 characterization 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 the curve of 0.77 (95% CI: 0.76–0.77) for predicting mortality [3]. A low 4C score ( $\leq 3$  out of 21) could rule out mortality with high confidence (negative predictive value 99%). A high 4C score ( $\geq 15$  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]. Although 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 front-line 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 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 shows 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, whereas 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 hospitalized patients, with scarce data available from primary care where these markers are frequently assessed. The differ-

ence in setting is an important but often overlooked factor as variations in the prevalence of the condition of interest affect practical test performance in terms of its positive and negative predictive value. The 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 gastrointestinal 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 a 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. First, most of the studies validating the use of combination markers have been relatively small [98, 99]. Second, there is a scarcity of head-to-head comparisons between novel combination markers and conventional inflammatory markers, rendering their incremental value unclear. Third, there is no standardization 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 being 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 bloodstream 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 characterize the troponin cut-offs for differentiating patients at the highest versus 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 progno-

sis rather than a practical risk stratification tool in COVID-19.

### B-type natriuretic peptides (BNP)

B-type natriuretic peptides (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 characteristics [120–128]. Moreover, the amalgam of evidence consists mainly of retrospective analyses or single-centred prospective cohorts [120–128]. There remain 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 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 do 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 hospitalization 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 the activation of the innate immunity to infection [168]. More specific causes such as thrombotic thrombocytopenic purpura and haemolytic uraemia syndrome 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

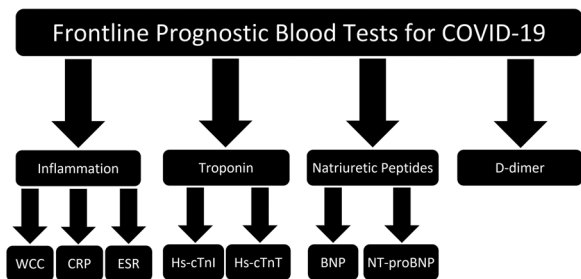
Before the COVID-19 pandemic, evidence suggested that vitamin D supplementation is associated with a small protective benefit against acute respiratory infections [172]. The arrival of COVID-19 sparked both further research interest and controversies. Some studies reported that vitamin D deficiency was linked to increased susceptibility to COVID-19 infections and longer duration of hospitalization [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], whereas 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 summarizes 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 (Fig. 3): (1) an *initial stage* when the patient becomes first infected and may display associated symptoms or remain asymptomatic [190]; (2) a *progressive stage* characterized 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



**Fig. 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.

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 (Fig. 3). Widespread screening and population-based education on symptomatology 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 lasts up to 2 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 PCT, 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, 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 hospitalization 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 hospitaliza-

tion 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 summarizes the possible dynamic changes in serum biomarkers during different stages of COVID-19.

### Markers of pulmonary dysfunction

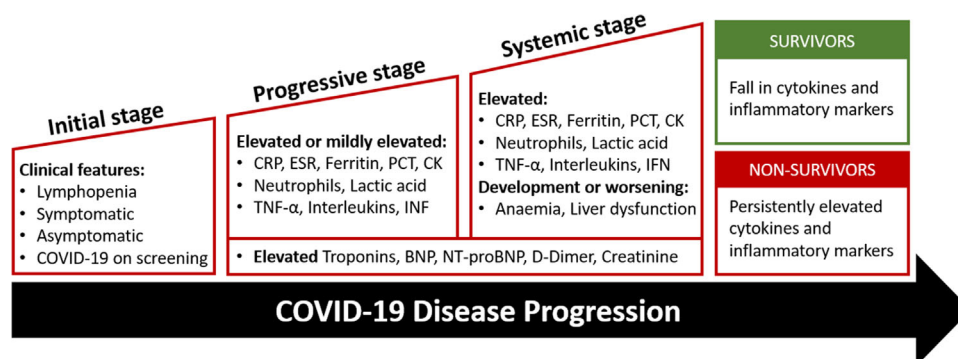
#### Peripheral oxygen saturation

As 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 the early detection of acute deterioration [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 ( $\text{PaO}_2$ ) are associated with an increased risk of adverse outcomes [213]. The  $\text{PaO}_2/\text{FiO}_2$  (the ratio of  $\text{PaO}_2$  and inhaled oxygen fraction) is an index used to assess the severity of ARDS, and a reduced  $\text{PaO}_2/\text{FiO}_2$  ratio has also been linked to an adverse prognosis in COVID-19 [213].  $\text{PaO}_2/\text{FiO}_2$  measured soon after admission predicts the risk for prolonged hospitalization [214] and the need for intubation [206, 215, 216].

Although both  $\text{PaO}_2$  and  $\text{PaO}_2/\text{FiO}_2$  are associated with requirement for intubation and



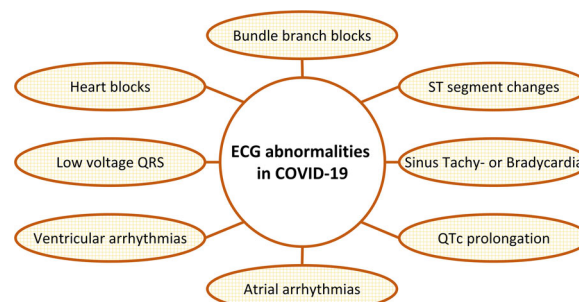
**Fig. 3** Summary of dynamic biomarker changes in different stages of coronavirus disease 19 (COVID-19) disease progression. BNP, B-type natriuretic peptide; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INF, interferons; NT-proBNP, N-terminal pro-B-type natriuretic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

artificial ventilation, controversy exists as to whether these parameters are suitable to dictate the necessity for artificial ventilation [217]. PaO<sub>2</sub> appears to be the most precise measure of oxygenation status [217], and PaO<sub>2</sub>/FiO<sub>2</sub> forms an important part of the ARDS definition [217]. However, any intubation decision is not solely dependent upon hypoxaemia [218], but rather a combination of clinical parameters, including increased work of breathing, hypercapnia and threatened airway owing to reduced conscious levels [218]. Therefore, although 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 optimize 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 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 reflect the inter-



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

stitial fluid status in pulmonary oedema [224, 225] and have 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)

Electrocardiogram (ECG) abnormalities are common in COVID-19 patients and are either related to underlying cardiovascular diseases or as a direct result of myocardial injury (Fig. 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] has 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 localize 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], whereas asystole and pulseless electrical activity are more common [252]. Several potential mechanisms may drive ventricular arrhythmias in COVID-19 [253–257]. First, 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]. Second, the COVID-19 inflammatory response can unmask clinically silent non-ischaemic cardiomyopathy, leading to VT storm [255]. Third, 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 corrected 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-threatening 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 (Fig. 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 mechanisms 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-day 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 utilization 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, the 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]. Although 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 hospitalization and protracted recovery can also lead to the 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] and 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-computed tomography (CT) findings in COVID-19 include bilateral ground-glass opacifications and lower lobe consolidation [297–300], whereas 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

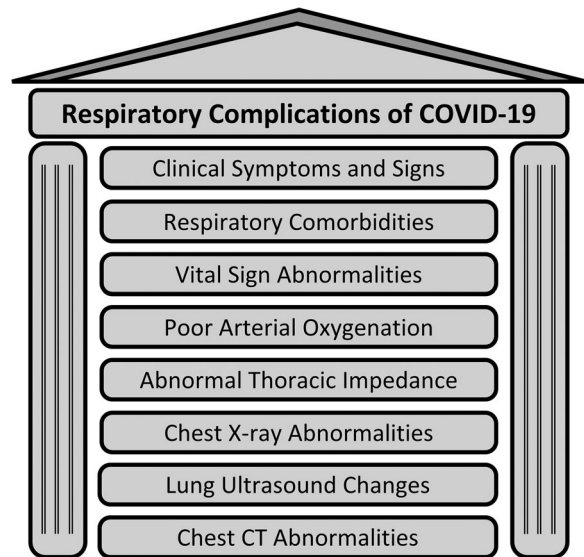
peripherally distributed ground-glass opacifications [302, 303], consolidation [304], anterior and paracardiac involvement [302], the ‘crazy paving pattern’ [302, 305] and pleural effusions [302]. More extensive opacifications involving multiple zones of the lung field and air bronchograms are also helpful 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]. Although 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 are 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 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 the 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



**Fig. 5** Biomarker assessment of respiratory complications related to coronavirus disease 19 (COVID-19). CT, computed tomography.

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 patients showed that patients with high CAC scores ( $\geq 300$ ) 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 in 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 the assessment of patients with chest pain, elevated cardiac troponins of unclear aetiology, possible intra-cardiac thrombi and for the 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 pro-

ocols 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 hospitalization, 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, transthoracic echocardiography (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, PE 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



	Stages of acute COVID-19 infection		
	Initial	Progressive	Systemic
History and Examination	■	■	■
Comorbidities	■	■	■
Vital signs	■	■	■
Arterial oxygenation	■	■	■
Electrocardiogram	■	■	■
Serum biomarkers	■	■	■
CXR	■	■	■
Chest CT	■	■	■
Lung ultrasound	■	■	■
Echocardiography	■	■	■

**Fig. 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 are known for certain modes of assessment such as clinical history, examination, vital signs, arterial oxygenation, electrocardiogram, serum biomarkers, chest X-ray (CXR), chest computed tomography (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 clear-cut biomarker abnormalities. Echocardiography may also be useful in the latter stages. Comorbidities are non-modifiable and relevant considerations in all stages.

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 Fig. 6.

### Cardiovascular magnetic resonance (CMR)

Cardiovascular magnetic resonance (CMR) offers a multi-parametric assessment of cardiac structure, function and myocardial tissue characterization [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 characterize 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 [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 hospitalization rates and mortality worldwide [350, 351]. Vaccination programs offer 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, lockdowns 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 health-care 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 materialize. 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 relies on there being accurate clinical risk stratification tools. Future clinical services that integrate AI 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 hospitalizations [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, the 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 because the majority of evidence is retrospective and prospective validation is required for their clinical translation.

### Author contributions

*Conceptualization – lead; resources – lead; writing – original draft – lead; writing – review and editing – lead:* Alexander Liu, Anthony R. M. Coates. *Conceptualization – equal; resources – equal; writing – original draft – supporting; writing – review and editing – supporting:* Robert Hammond, Peter D. Donnelly, Juan Carlos Kaski.

### Conflict of interest statement

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