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PREDICTING A WORSE COVID-19 OUTCOME

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8 May 2020

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There is now considerable, rapidly evolving literature regarding risk factors for, or predictors of, severe COVID-19 disease. This paper attempts to summarise these with an emphasis on recent, consolidated findings (where possible), broadly categorised into host factors, co-morbidities, and laboratory variables that predict a worse outcome.

Identification and knowledge of these characteristics and disease markers might help reduce the risk of critical illness, requirement for intensive care and ventilation, and ultimately of death. Reported odds ratios or hazards ratios are largely derived from systematic reviews/meta-analyses or large cohort studies only.

HOST FACTORS

- Gender. Male OR = 1.76, CI [1.41, 21.8][1]. OR = 3.82, CI [1.28, 11.44] even when adjusting for the presence of co-morbidities[2].

  > This might be due to protection conferred by sex hormones or the X chromosome which play a role in innate and adaptive immunity, hormone-modulated ACE2 expression, risk of venous thromboembolism[3], or less association of females with bad lifestyle habits such as smoking[1]. The same gender difference was found in MERS-CoV and SARS-CoV[2].

- Age. Older than 65(OR = 6.06, CI [3.98, 9.22][1]. Older than 60 years OR = 8.55, CI[1.63, 44.86][4,5]. Older than 75 years HR = 3.43, CI [1.24, 9.50][6]. Increasing odds of in-hospital death OR = 1.10, CI [1.03, 1.17] per year increase[7].

  > The age effect is thought to relate to the increasing frequency of co-morbidities and decline in immunity[1].

- Smoking status. Current smoker OR = 2.51, CI [1.39, 3.32][1]. Any history of smoking OR = 14.29, CI [1.58, 25.0][4].

- Longer waiting time between symptom onset and hospitalisation HR = 1.05, CI [1.01, 1.08][8].

CO-MORBIDITIES

- Hypertension OR = 2.72, CI [1.60, 4.64][1]. OR = 3.05, CI [1.57, 5.92][9].

  > The proposed pathobiologic mechanism is perhaps via ACE2 or immune dysregulation which occurs in hypertension[9].

- Diabetes OR = 3.68, CI [2.68, 5.03][1]. Diabetes mellitus is associated with mortality, severe disease presentation, ARDS and disease progression in COVID-19 (Relative Risk = 2.38 [1.88, 3.02], p<0.001[10] and ICU admission OR = 2.79, [1.85, 4.22][11]).

- Cardiovascular/Coronary heart disease OR = 5.19, CI [3.25, 8.29][1]. Coronary heart disease HR = 4.28, CI [1.14, 16.13][6].

  > The pathobiologic hypothesis in cardiac disease is that decline in cardiac function and lower immunity in such patients confers vulnerability[1]. Moreover, ACE2 expression (the receptor binding site on cells for SARS-CoV-2) is upregulated in failing heats[9].

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- Respiratory disease OR = 5.15, CI [2.51, 10.57][1]. Specifically for patients with COAD the risk of developing severe COVID-19 infection was higher, OR = 4.38 [2.34, 8.20][12].
  > Pre-existing lung disease increases the risk of (any) infection but also the risk of developing Acute Respiratory Distress Syndrome (ARDS)[1].

- Cerebrovascular disease HR = 8.72, CI [1.07-8.94][6].

- Pre-existing cancer. There are several case reports of higher mortality and/or higher rates of severe disease/intubation among patients (without greater mortality) with pre-existing cancer[13,14].
  > Patients with cancer have impaired immune systems, baseline fragility, and procoagulant states[13].

- Obesity (BMI > 30)
  > Chronic, low-grade inflammation characterised by increased levels of several pro-inflammatory cytokines predisposes to a greater risk of infection and more adverse outcomes, together with complementary hyperactivation and presence of co-morbidities[15,16]. By extension, higher cardiopulmonary fitness may reduce the risk, duration, and severity of viral infections[15].

- Vitamin D deficiency may confer a greater risk of developing more severe COVID-19 infection. There is observation data suggesting countries that lie below 35 degrees North have low mortality – this being the latitude above which people do not receive sufficient sunlight to retain adequate vitamin D levels[17,18]. Vitamin D deficiency is associated with hypertension, diabetes, increased rate of respiratory infections and obesity, as well as being important in regulating and suppressing inflammatory cytokines and macrophages. There are multiple confounders in interpreting these observations and it does not suggest higher doses than normal are helpful in COVID-19[18].

- The extent of change on the CT chest scan with more frequent consolidation and air bronchograms all predict a worse outcome[19,20]. There are also higher incidences of lymphadenopathy, pericardial effusions and, more rarely, pleural effusions in those with severe disease[21].

DISEASE CHARACTERISTICS

- Absence of fever (<37.3) OR = 0.56, CI [0.38, 0.82][1].
  > The pathobiologic hypothesis is that impaired immunity is associated with low or absent fever[1].

- Dyspnoea OR = 4.16, CI [3.13, 5.53][1]. (HR = 3.96, CI [1.42, 11.0][6].
  > The presence of dyspnoea suggests greater disruption to gas exchange with impaired respiratory function and more severe respiratory disease[1].

- Unremitting viral shedding[7], which is closely related to IL-6 levels[22].

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LABORATORY PARAMETERS

Markers of organ dysfunction

- Elevated AsT (>40U/L) OR = 4.00, CI [2.46, 6.52][1]. HR= 2.2, CI [1.1-6.73][6].
  > Elevated AsT is a marker of multiorgan dysfunction[1].

- Elevated creatinine (>=133mol/L) OR = 5.30, CI [2.19, 12.83][1].
  > Elevated creatinine is a marker of multiorgan dysfunction and specifically renal dysfunction[1]. Similarly, the presence of haematuria and/or proteinuria (markers of renal impairment as well as systemic inflammation) is similarly predictive[23].

- Elevated high-sensitive Troponin I (>28pg/mL) OR = 43.24, CI [9.92, 188.49]1. Elevated highly-sensitive Troponin T OR = 6.63, CI [2.24, 19.65][24].
  > SARS-CoV-2 can cause direct myocardial injury through cardiomyocyte infection via ACE2 receptor, but also indirectly via the inflammatory storm[1].

- Elevated NT-pro BNP/BNP. Conflicting data currently confuses whether elevation is truly associated with a more severe disease course[9]. There is a suggestion of a higher NT-proBNP predicting a poor outcome with threshold of 88.64pg/mL HR = 1.37, CI [1.22-1.54][25].

- Elevated LDH (>245U/L) OR = 8.86, CI [2.72, 28.89][1].

- Elevated D-Dimer >0.5mg/L OR = 4.81, CI [1.47, 15.69][1]. D-Dimer >1.0ug/mL OR = 18.42, CI [2.64, 128.55][6].
  > Current studies have shown that many COVID-19 patients have abnormal coagulation function. Monocytes and tissue cells are activated after injury, causing the release of cytokines and the expression of tissue factors, and finally causing hypercoagulability of blood[1,26] and disseminated intravascular coagulation (DIC)[8]. This will increase the risk of thrombosis and greater likelihood of ischemia and hypoxia due to the embolisation of the viscera, leading to progression of disease to critical disease or death[1]. Other trials have shown consistent results across different threshold cut-offs[27]. Clearly, coagulation profile markers of DIC also remain relevant in this context e.g. PT, APTT, FDP, fibrinogen.

- Higher sequential organ failure assessment (SOFA) score OR = 5.65, CI [2.61, 12.23][6].
  > SOFA score is a good diagnostic marker for sepsis and septic shock and also reflects the state and degree of multi-organ dysfunction[6].

Markers of infection and inflammation

- Elevated procalcitonin (>0.5ng/mL) OR = 8.21, CI [1.92, 35.05][1]. HR = 8.72, CI [3.42-22.28]. HR = 4.91, [1.80-13.40][28]. A recent pooled meta-analysis suggested increased procalcitonin was predictive of a poor outcome and disease progression OR = 4.76 CI [2.74-8.29] when above the normal reference range[29].
  > Procalcitonin is a glycoprotein that is usually low/undetectable, but levels are increased classically by bacterial infection[28].

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- **Elevated C-reactive protein,** CRP>8.2mg/L OR = 10.53, CI [1.22, 34.70]. Alternatively CRP >41.8mg/L HR = 4.39, CI [1.92, 10.03][28]. There is some evidence that CRP increases significantly in the initial stage of severe infection e.g. before chest imaging and other blood parameters[30].
  > Elevated CRP is an important inflammatory index and also marker of abnormal coagulation[3].

- **Reduced albumin** <40g/L OR = 7.35, CI [1.10, 50.0][3].
  > Pathobiologic hypothesis reflects the role of albumin in inflammation and as a marker of the nutritional status of the patient, when low suggesting a loss of resistance to the virus[3].

- **Elevated white cell count** (>4 x 10 to 9th / L) OR = 0.30, CI [0.17, 0.51][1].
  > Various studies indicate the white cell count is normal or low in the early stages of disease[1]. There may, however, be publication bias in white blood cell count results[31].

- **Lymphopaenia**[32]. (Weight mean difference 0.29 (109/L), CI [0.22, 0.36][31] and **Neutrophil count** (Weight mean difference -1.57 (109/L), CI [-2.60, -0.54][31]. There is correlation between a lower level of lymphocyte subsets CD3+ (cut-off 576), CD4+ (cut-off 391), CD8+ (cut-off 214) with a more severe clinical course[33]. In another series, CD4+ T cell counts on admission were independently associated with early PCR conversion (HR = 1.07 per 100cells/uL increase, p=0.02)[34]. A low lymphocyte percentage below 20% at presentation also predicts a worse outcome, but when assessment is repeated at day 17-19, patients with a lymphocyte percentage <5% predict ICU requirement and/or a worse outcome[35].

- **Elevated soluble urokinase plasminogen activator receptor** (suPAR) >=6ng/mL HR = 16.43, CI [4.56, 59.19][36].
  > Endothelium activation (as evidenced by elevated D-dimer) is associated with cleavage of urokinase plasminogen activator receptor bound on the surface leading to an increase in the soluble counterpart. It has been trialled as a biomarker for death among patients admitted to the emergency department and in sepsis[36].

- **Elevated Interleukin-6** is associated with an adverse outcome[37]. A cut-off of >32.1pg/mL has been proposed HR = 2.78, CI [1.06, 5.33][28].
  > High IL-6 is a common feature in cytokine release syndrome patients/cytokine storm which in turn may propagate multi-organ dysfunction[8].

- **Low-density lipoprotein levels** are low at presentation but continuously decline if a more severe disease progression pathway occurs OR = 4.48, CI [1.55, 12.92][38]. Patients that recover show an improvement in LDL levels to baseline levels.
  > Aberrant LDL levels in more severe COVID-19 infection may result from liver injury, inflammatory-induced oxidation of LDL, and increased vascular permeability[38].

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- Elevated ferritin is associated with death from COVID-19 and development of ARDS HR = 3.53, [1.52, 8.16][6].

- Thrombocytopaenia at admission is associated with three-times as high mortality[39]. An increment of per 50 x 10^9/L in platelets was associated with a 40% reduction in mortality HR = 0.60, [0.43-0.84].

There is some conflict regarding whether immunosuppression causes a more severe disease trajectory with worse outcome. In the most recent systematic review of 16 studies, which encompassed only 110 immunosuppression patients (mostly cancer), it was noted that cancer was more often associated with a more severe course without necessarily greater motrality[40]. Overall, immunosuppressed patients in this small series had a more favourable disease course, perhaps due to a weaker, less destructive immune response.

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