Risk factors associated with severe disease and death in COVID-19 patients

Introduction
COVID-19 can affect anyone, and the disease can cause symptoms ranging from mild to very severe. However, some people may be more likely to have severe illness than others because they have characteristics or medical conditions that increase their risk. Given that the burden to the health system due to COVID-19 is a consequence of the disease severity, it is important to identify these risk factors in order to find at-risk individuals and develop prevention and treatment measures appropriate to these groups. Once identified, information on the proportion of high-risk individuals will also inform government responses in managing healthcare resources according to the burden of disease. This information can also inform plans to identify and protect the vulnerable in the society especially when countries are loosening initial restrictions.

Evidence from China, Italy, France and the UK identified several risk factors such as older age (>65 years), male gender, the presence of co-morbidities and certain clinical manifestations (e.g. shortness of breath and fever) as some of the key risk factors associated with severe illness or death\(^1\)\(^-\)\(^4\). Table 1 summarizes findings from systematic reviews and meta-analyses conducted to synthesize evidence on COVID-19 risk factors.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Study</th>
<th>Odds/Risk ratio (95% CI)</th>
<th>What it means</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>Zheng et al.</td>
<td>OR = 6.06 (3.98 - 9.22), P &lt; 0.00001</td>
<td>Disease progression (to critical state and death) was 6.06 times more likely in older individuals (&gt;65 years) compared to younger ones</td>
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<td></td>
<td>Parohan et al.</td>
<td>OR= 4.59 (2.61 – 8.04), p&lt;0.001</td>
<td>Individuals older than 65 years were 4.59 times more likely to die from COVID-19 compared to those younger than 65 years</td>
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<tr>
<td>Male gender</td>
<td>Martins-Filho et al.</td>
<td>RR=1.3 (1.1 - 1.4), p &lt; 0.001</td>
<td>Being male increased the risk of mortality 1.3 times compared to being female</td>
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<td></td>
<td>Zheng et al.</td>
<td>OR = 1.76 (1.41 - 2.18), P &lt; 0.0001</td>
<td>Disease progression (to critical state and death) was 1.76 times more likely in men compared to women</td>
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<td></td>
<td>Abate et al.</td>
<td>RR=1.63(1.33-1.99), p=0.000</td>
<td>Being male increased the risk of mortality 1.63 times compared to being female</td>
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<td>Co-morbidities</td>
<td>Espinosa et al.</td>
<td>OR=2.4, (1.7-3.3) p=0.00001</td>
<td>The risk of death for a patient with a comorbidity compared to one with no comorbidity was 2.4 higher</td>
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<td></td>
<td>Abate et al.</td>
<td>RR= 2.20(1.75 - 2.77)</td>
<td>Mortality among hospitalized patients with COVID-19 was two times more likely in patients with any co-morbidity as compared to those who didn’t have co-morbidities</td>
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<td></td>
<td>Martins-Filho et al.</td>
<td>RR= 1.6, 95%CI 1.4 - 2.0</td>
<td>The risk of in-hospital death for patients with co-morbidities was 1.6 times higher</td>
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<tr>
<td>Clinical manifestation</td>
<td>Zheng et al.</td>
<td>shortness of breath: OR=4.16, (3.13-5.53), P &lt; 0.00001</td>
<td>Patients with fever are 4.16 times more likely to progress to severe disease</td>
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<td></td>
<td>Shi et al.</td>
<td>Shortness of breath: OR = 4.34 (2.68–7.05), P &lt; 0.001</td>
<td>The risk of mortality in patients with shortness of breath was 4.34 times higher</td>
</tr>
<tr>
<td></td>
<td>Martins-Filho et al.</td>
<td>Shortness of breath: RR=1.8, (1.4 - 2.2)</td>
<td>The risk of in-hospital death for patients with shortness of breath was 1.8 times higher</td>
</tr>
</tbody>
</table>

Key Messages
- While everyone is at risk of SARS-CoV-2 infection, some people may be more likely to progress to severe illness than others because they have characteristics or medical conditions that increase their risk.
- The major risk factors associated with severe disease and death include older age (>65 years), male gender and the presence of comorbidities.
- Comorbidities such as heart disease, hypertension, diabetes and chronic obstructive respiratory disease are the most common in COVID-19 deaths but HIV-1 and TB infection are also associated with increased risk of death from COVID-19 in Africa.
- It is important to ensure that all persons at high risk of developing severe disease and mortality are identified to facilitate prompt access to health facilities and appropriate supportive care and to inform prevention strategies.
Age
Increasing evidence has shown that older patients are more likely to develop severe illness and have a higher risk of in-hospital death\(^1\text{-}^5\). For example, over 95 per cent of fatalities due to COVID-19 in Europe have been of people aged 60 years or older. In the United States, 80\% of deaths were among adults aged 65 years and older.

Gender
Men were found to be more likely to develop critical illness and succumb to COVID-19 compared to women\(^6\text{-}7\). Mortality data from China, Italy and the USA show that majority of deaths recorded were in men\(^2\text{-}5\text{,}8\).

Existing co-morbidities/underlying health conditions
The most commonly reported conditions that put patients at higher risk of severe disease and mortality were\(^7\text{-}9\text{-}12\):

1. Diabetes,
2. Hypertension,
3. Chronic lung disease, and
4. Cardiac disease

In the South African province of the Western Cape, HIV-1 and TB infection are associated with 2-2.5 times higher risk of COVID-19 death\(^13\). Additionally, presence of more than one co-morbidity was associated with poorer clinical outcomes\(^14\).

Clinical manifestations
Symptoms of COVID-19 could also be predictors of severe disease and death. Patients with shortness of breath (dyspnea) were more likely to progress to critical illness or even die\(^6\text{-}15\).

Conclusion
Older age, male gender, presence of co-morbidities and dyspnea are risk factors for severe disease and mortality. Identification of high-risk populations is important to reduce COVID-19 mortality. Firstly, it allows governments to make projections of the likely burden on the health system (e.g. capacity of critical care facilities) and implement necessary surge measures; and secondly, it informs the planning and implementation of strategies that can reduce transmission or poor outcomes in high-risk populations. Such strategies, known as shielding, involves minimizing interaction between high risk individuals such people over 65 years and those with comorbidities. However, this strategy is not feasible if a significant proportion of the population are shielded. In LMICs the feasibility of shielding should be addressed since rural areas are typically characterized by multigenerational households. Additionally, informal settlements, forced displacement camps (refugee, internally displaced), and low-income setting housing arrangements make it difficult to isolate vulnerable individuals because of the need to share amenities (such as toilets) and even sleeping rooms. It is therefore pertinent that a thorough assessment of the feasibility of shielding strategies is carried out. Information on high risk groups can also be used in the future when a vaccine is available in order to prioritize vaccination based on risk. Research on treatments should explore how to mitigate for the risk factors.

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References


