Impact of age, gender and comorbidities affecting the severity of COVID-19 infection in Kashmir

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ABSTRACT

Aim: To study the impact of age, gender and comorbidities/risk factors affecting the severity of CoronaVirus Disease 2019/Severe acute respiratory syndrome coronavirus 2 (COVID-19/SARS-COV-2) infection in the Kashmiri community. **Materials and Methods:** The present descriptive cross-sectional study was conducted in the Chest Disease Hospital. The study included 957 subjects who were diagnosed with SARS-CoV-2 infection. Descriptive statistics were calculated. **Results:** In the age group <40 years, the severity of illness was found to be 30.42% and the occurrence of death was 11.54%, in the 40–60 years, the severity of the illness was found to be 32.51% and the occurrence of death was 12.84%, in the older age >60 years, the severity of illness was found to be 35.74% and the occurrence of death was 10.49%. In males, the severity of the illness was found to be 32.39% and the occurrence of death was 11.27%. In females, the severity of the illness was found to be 33.96% and the occurrence of death was 12.58%. In patients suffering from chronic obstructive pulmonary disease (COPD), asthma, diabetes mellitus, coronary artery disease (CAD), chronic kidney disease (CKD), cancer, hypertension, chronic liver disease (CLD), cerebrovascular disease, thyroid disease, steroid use, obstructive sleep apnoea (OSA) and smokers, the severity of the illness was 29.27, 41.67, 37.73, 20, 23.53, 11.11, 36.30, 40, 20, 36.37, 50, 54.54 and 36% and the occurrence of death was 14.63, 0, 10.69, 10, 11.76, 5.55, 10.67, 0, 0, 20.78, 0, 0 and 16%, respectively. **Conclusion:** The age, gender and comorbidity disparities seen in the COVID-19 vulnerability emphasise the need to understand the impact of these factors on the incidence and case fatality of the disease.

Keywords: Age, comorbidities, COVID-19/SARS-COV-2, gender

Introduction

In late 2019, an outbreak of pneumonia with unknown aetiology was found in Wuhan, China. Then the pathogen was isolated soon and called the 2019 novel coronavirus. At present, this disease is spreading rapidly and taking a heavy toll on the health and economy worldwide. It is of utmost importance to understand the nature of this disease to identify and combat it better.[1]

Huang et al.[2] mentioned the clinical features of 41 confirmed patients, and indicated that 13 (32%) of them had underlying diseases including cardiovascular disease, diabetes, hypertension and chronic obstructive pulmonary disease (COPD). Subsequently, Wang et al.[3] presented findings from 138 cases of COVID-19/SARS-CoV-2 and the results suggested that 64 (46.4%) of them had comorbidities. Sattar et al.[4] carried out a study on the association of body mass index (BMI) and the future risk of COVID-19 infection and BMI was associated strongly with a positive test and the risk of death related to the COVID-19 disease. The gradient of the risk in relation to the BMI was steeper in those under 70 years of age, compared with those aged 70 years or older for the COVID-19/SARS-COV-2 related death.

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Reports have shown no major sex differences in the absolute number of confirmed COVID-19 cases in those countries where sex-disaggregated data were available. However, an equal absolute number of cases in women and men may point towards a higher incidence in men in the older age groups.[5] Since the data were contradictory, we aimed to synthesise the evidence to associate age, gender and comorbidities with the severity of the COVID-19/SARS-CoV-2 infection and mortality rate.

Methodology

A retrospective, single-centred study including the participants with laboratory-detected SARS-CoV-2 infection admitted to the designated COVID-19 centre in a tertiary care hospital from March to October 2020 was done. Clinical records, laboratory data, and radiological findings were analysed. The impact of age, gender, BMI and comorbidities of these participants were evaluated to analyse their association with the severity of the COVID-19 infection in them.

The patients were classified into three age groups, including the young COVID-19 group: Age <40 years (286 patients), middle-aged COVID-19 group: Age 40–60 years (366 patients) and older COVID-19 group: Age >60 years (305 patients); 957 patients were admitted out of which 639 were males and 318 were females.

The comorbidities that were enquired about were COPD, asthma, diabetes mellitus, coronary artery disease (CAD), chronic kidney disease (CKD), cancer, hypertension, chronic liver disease (CLD), cerebrovascular disease, thyroid disease, steroid use, obstructive sleep apnoea (OSA) and tobacco smoker.

Severe-symptomatic cases were defined as the participants who had clinical symptoms of pneumonia (dyspnoea, tachypnoea, peripheral capillary oxygen saturation <93%, and needed oxygen therapy). The deceased patients were also included in the study.

The influence of age, gender and comorbidities/risk factors on the severity of the COVID-19 infection and death rate were analysed.

The study was approved by the institutional ethics committee vide reference no: IEC-GMC-Sgr/29 dated 23/02/2021.

Results

Out of the 957 patients, the young COVID-19 group <40 years included 286 patients and the severity of illness was found to be 30.42% (*P* value = 0.428) and the mortality was 11.54% (*P* value = 0.93). In the middle-aged COVID-19 group of 40–60 years which included 366 patients, the severity of the illness was found to be 32.51% (*P* value = 0.889) and the mortality was 12.84% (*P* value = 0.57). In the older-aged COVID-19 group > 60 years which included 305 patients, the severity of the illness was found to be 35.74% (*P* value = 0.36) and the mortality

was 10.49% (*P* value = 0.56) Explained in [Figure 1 and Table 1].

Out of the 957 patients, 639 were males in whom the severity of illness was found to be 32.39% (*P* value = 0.62) and the mortality was 11.27% (*P* value = 0.55); 318 patients were females in whom the severity of illness was found to be 33.96% (*P* value = 0.62) and the mortality was 12.58% (*P* value = 0.55) [Table 2 and Figure 2].

In 41 patients suffering from COPD, the severity of illness was 29.27% (*P* value = 0.3) and the mortality was 14.63% (*P* value = 0.56). In 12 patients suffering from asthma, the severity of illness was 41.67% (*P* value = 0.11) and the mortality was 0.00% (*P* value = 0.20). In 159 patients suffering from diabetes mellitus, the severity of illness was 37.73% (*P* value = 0.008) and the mortality was 10.69% (*P* value = 0.71) and both these findings were significant. In 20 patients suffering from CAD, the severity of illness was 20.00% (*P* value = 0.93) and the mortality was 10.00% (*P* value = 0.81). In 17 patients suffering from CKD, the severity of illness was 23.35% (*P* value = 0.80) and the mortality was 11.76% (*P* value = 0.99). In 18 patients suffering from cancer, the severity of illness was found to be 11.11% (*P* value = 0.35) and the mortality was 5.55% (*P* value = 0.42). In 281 patients who were suffering from hypertension, the severity of illness was 36.30% (*P* value = 0.01) which was a significant finding and the mortality was 10.67% (*P* value = 0.63). In five patients who were suffering from CLD, the severity of illness was found to be 40.00% (*P* value = 0.32) and the mortality was 0.00% (*P* value = 0.41). In 10 patients suffering from cerebrovascular disease, the severity of illness was found to be 20.00% (*P* value = 0.955) and the mortality was 0.00% (*P* value = 0.25). In 77 patients suffering from the thyroid disease, the severity of illness was found to be 36.37% (*P* value = 0.32) and the mortality was 20.78% (*P* value = 0.019) and both the findings were found to be significant. In four patients using steroids, the severity of illness was found to be 50.00% (*P* value = 0.015) and the mortality was 0.00% (*P* value = 0.46). In 11 patients who were suffering from OSA, the severity of illness was found to be 54.54%% (*P* value = 0.015) which was a significant value and the mortality was 0.00% (*P* value = 0.22). In 50 smoker patients, the severity of illness was found to be 36.00% (*P* value = 0.05) and the mortality was 16% (*P* value = 0.36) [Table 3].

Discussion

In this study, it was found that the severity of illness increased with the increasing age while more deaths were seen in the 40–60 year-age (middle age) group as compared to the other age groups although the association was not found significant. The COVID-19/SARS-CoV-2 morbidity and mortality were higher in the older people. Overall, in Asia, Europe and the US, 80% of severe outcomes associated with the COVID-19 disease were observed among adults aged more than 65 years.[6] Ageing is linked with an increasing decline and dysregulation in the immune functions and produces a systemic, chronic and

Table 1: Comparison and association of the severity of illness and death rate with age				
	Severity of illness prevalence (%)	Mortality (%)	*P* of the severity of an age group with the other age group	*P* of death of an age group with the other age group
<40 years (*n*=286)	30.42%	11.54%	0.428	0.93
40-60 years (*n*=366)	32.51%	12.84%	0.889	0.57
>60 years (*n*=305)	35.74%	10.49%	0.36	0.56

Table 2: Comparison and association of the severity of illness and death rate with gender				
	Severity of illness prevalence (%)	Mortality (%)	*P* of the severity of a gender with the other gender	*P* of death of a gender with the other gender
Male (*n*=639)	32.39%	11.27%	0.62	0.55
Female (*n*=318)	33.96%	12.58%	0.62	0.55

Table 3: Comparison and association of the severity of illness and death rate with associated conditions/comorbidities/risk factors				
Presence of associated conditions/co morbidities	Severity of illness prevalence (%)	Mortality (%)	*P* of severity of a comorbidity with the population	*P* of death of a comorbidity with the population
COPD (*n*=41)	29.27%	14.63%	0.30	0.56
Asthma (*n*=12)	41.67%	0.00	0.11	0.20
Diabetes mellitus (*n*=159)	37.73%*	10.69%	0.008	0.71
CAD (*n*=20)	20.00%	10.00%	0.93	0.81
CKD (*n*=17)	23.53%	11.76%	0.80	0.99
Cancer (*n*=18)	11.11%	5.55%	0.35	0.42
Hypertension (*n*=281)	36.30%*	10.67%	0.01	0.63
CLD (*n*=5)	40.00%	0.00	0.32	0.41
Cererovas. dis. (*n*=10)	20.00%	0.00	0.955	0.25
Thyroid disease (*n*=77)	36.37%*	20.78%*	0.32	0.019
Steroid use (*n*=4)	50.00%	0.00	0.17	0.46
OSA (*n*=11)	54.54%*	0.00	0.015	0.22
Smoker (*n*=50)	36.00%*	16.00%	0.05	0.36

low-grade proinflammatory response called inflammaging. It can also be deduced from the greater number of deaths in the 40–60 age group that they might have been admitted late when the condition was worse, thus, worsening the outcome.

The most interesting finding of our analysis was that severe obesity is a factor for severe respiratory disease and death in inflammaging hospitalised patients with COVID-19.

The number of males admitted was twice that of the females but it was found that the females who were admitted had a slightly higher severity of illness and a greater number of deaths but the difference was not significant.

Raimondi F *et al.*[7] conducted an observational study of the COVID-19 patients during the first 3 weeks of the outbreak. Overall, 28-day mortality was 26.1% in women and 38.1% in men (*P* = 0.018). Gender was not seen to be an independent predictor of death once the parameters related to the severity of the disease at presentation was included in the multivariable analysis (*P* = 0.898).

In patients suffering from OSA syndrome, the severity of the illness was 54.54% which was significant but there was no

mortality. The angiotensin-converting enzyme 2 (ACE-2) is the entry receptor of SARS-CoV-2 and an increased expression of the angiotensin-converting enzyme (ACE) in untreated OSA patients due to chronic intermittent hypoxia has been shown. Fibrosis can also be seen after COVID-19 and it was previously shown to be a risk factor for OSA. Therefore, keeping in mind the modulating effects of sleep on the immune system, proper treatment of OSA patients may be protective/beneficial in COVID-19. Second, patients who suffered from COVID-19/SARS-COV-2, particularly severe cases, may be at risk for OSA due to pulmonary fibrosis.[8]

In four patients on steroids, the severity of illness was 50% which was significant but there was no mortality. Short-term corticosteroid use is associated with generally mild side effects while long-term corticosteroid use may be associated with serious sequelae, including osteoporosis, aseptic joint-necrosis, gastrointestinal, hepatic, adrenal insufficiency and ophthalmologic effects.[9]

In 12 patients suffering from asthma, the severity of the illness was 41.6% and there was no mortality. Izqueirdo *et al.*[10] conducted a study and found that patients with asthma and COVID-19 were older and at increased risk due to comorbidity-related factors.
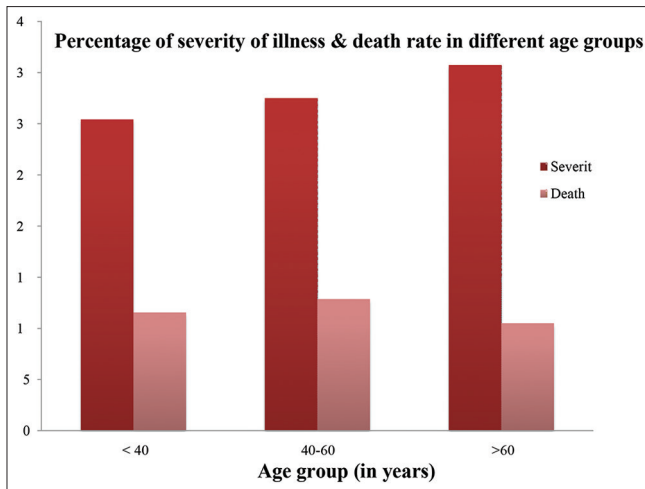
Figure 1: Percentage of severity of illness and death rate in different age groups

Figure 2: Percentage of severity of illness and death rate in males and females

In 159 patients suffering from diabetes mellitus, the severity of the illness was 37.73% (*P* value = 0.008) and the mortality was 10.69% (*P* value = 0.71). The two nationwide studies done by Guan *et al*.[11] reported a higher prevalence of Type-2 diabetes mellitus among the patients with severe disease versus non-severe disease. Likewise, Zhu *et al*.[12] reported a higher prevalence of Type-2 diabetes mellitus in patients with severe disease versus without severe disease.

In 77 patients suffering from thyroid disease, the severity of the disease was found to be 36.37% (*P* value = 0.32) and the mortality was 20.78% (*P* value = 0.019).

Based on a contrite meta-analysis data, thyroid disease was seen to be associated with an enhanced risk of severe COVID-19/ SARS-COV-2 infection. Many reasons can be proposed to explain this result. First, the thyroid hormone is important in the regulation of an innate immune response. Therefore, an excess or deficiency of the thyroid hormone levels observed in the thyroid disease will lead to dysregulation of an innate immune response.[13]

In five patients suffering from CLD, the severity of the illness was found to be 40.00% (*P* value = 0.32) and the mortality was 0.00% (*P* value = 0.41). Dong JI *et al*.[14] found that the disease progression is significantly higher in COVID-19 patients with CLD as compared to those with no CLD.

In 281 patients suffering from hypertension, the severity of the illness was 36.30% (*P* value = 0.01) and the mortality was 10.67% (*P* value = 0.63). According to a retrospective study/analysis consisting of 487 COVID-19/SARS-COV-2 patients in the Zhejiang Province of China, the prevalence of hypertension was higher in the 49 severe cases than in the 438 mild cases (53.1% vs. 16.7%, *P* < 0.0001).[15]

Leung *et al*.[16] conducted a recent study published in the European Respiratory Journal and reported a higher expression of the
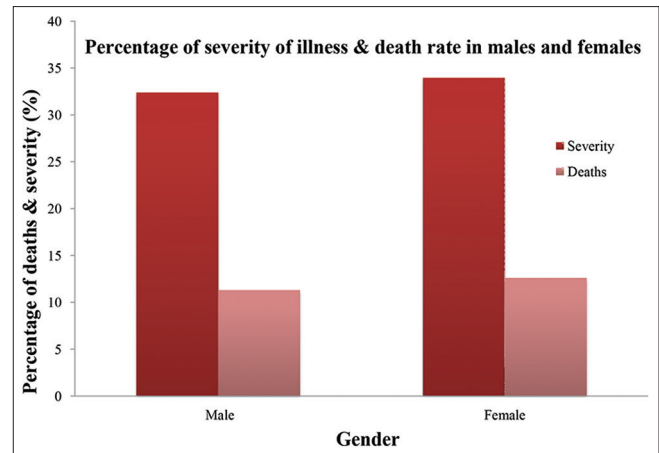
protein ACE-2 in the small airway epithelia of the smokers and COPD patients with putatively important implications for COVID-19/SARS-COV-2 patients since the ACE-2 has been shown to be the receptor utilised by SARS-CoV-2 to enter the host cell. Furthermore, the authors reported that the current smokers had a higher expression of ACE-2 gene expression than the non-smokers concluding that the increased ACE-2 expression in the smokers might predispose to an increased risk of COVID-19/SARS-CoV-2 infection.

In 41 patients suffering from COPD, the severity of illness was 29.27% (*P* value = 0.3) and the mortality was 14.63% (*P* value = 0.56). People with COPD who were prescribed Inhaled corticosteroids (ICSs) were at an increased risk of COVID-19-related deaths compared with those prescribed Long acting beta-agonists (LABA)-Long acting muscarinic antagonists (LAMA) combinations (adjusted HR 1·39 [95% CI-1·10–1·76]). In comparison with those patients who were prescribed Short-acting beta-agonists (SABAs) only, people with bronchial asthma who were prescribed a high dose of ICS were at an increased risk of death (1·55 [1·10–2·18]), whereas those given a low or medium dose were not (1·14 [0·85–1·54]).[17]

In 20 patients suffering from coronary artery disease (CAD), the severity of the illness was 20.00% (*P* value = 0.93) and mortality was 10.00% (*P* value = 0.81). The COVID-19 patients with pre-existing heart diseases may suffer a heart attack/myocardial infarction or develop congestive heart failure. This is due to a combination of the severe viral illness and its increased demands on the heart, increased heart rate compounded by low oxygen saturation due to respiratory symptoms, myocarditis and increased propensity for blood clot formation. In addition to the increase in these heart problems, a more unusual condition called myocarditis has also been observed in the COVID-19/SARS-COV-2 patients. In addition, some patients with underlying cardiovascular disease (CVD) might have an increased risk of mortality.[18]

In 17 patients suffering from CKD, the severity of illness was 23.35% (*P* value = 0.80) and the mortality was

11.76% (*P* value = 0.99). The CKD patients have a high risk of symptomatic COVID-19 infection, mainly due to impaired immune response, chronic inflammation, increased oxidative stress, uremic toxin accumulation and endothelial dysfunction. Collado *et al.*[19] presented a case series with seven patients suffering from CKD in which the Estimated Glomerular filtration rate (eGFR) was between 12 and 20 mL/min during the month prior to the COVID-19/SARS-COV-2 infection. The three major symptoms were fever, cough and dyspnoea, and five patients showed bilateral pneumonia. Hydroxychloroquine, ceftriaxone, azithromycin and corticosteroids were the most frequently prescribed drugs. Two patients needed non-invasive (NIV) mechanical ventilation (MV). The patients showed minimal-to-moderate renal function deterioration during admission, with an eGFR decline below 5 mL/min in six of the cases. Among which none required acute dialysis. Six patients were discharged alive and remained dialysis-free at the time of reporting, and one 76-year-old patient died.

In 18 patients suffering from cancer, the severity of illness was found to be 11.11% (*P* value = 0.35) and the mortality was 5.55% (*P* value = 0.42).

The risk of mortality in the cancer patients with COVID-19 infection was found 21.1% (95% CI: 14.7–27.6). Leave-one-out analysis showed risk estimates, which ranged from 19.1 to 22.8% upon removal of individual studies. Comparative analysis using six studies showed that the cancer patients had a significantly higher risk of mortality (OR = 3.23; 95% CI: 1.71–6.13; *P* = .0003; *n* = 10,841) than the non-cancer patients [Figure 3]. The combined studies were heterogeneous (*P* < .0001). The heterogeneousness was resolved by excluding the study by Miyashita *et al.*[20] while maintaining the significance of the effect estimate (OR = 4.11; 95% CI: 2.28–7.41; *P* < .00001) severe/critical COVID-19 disease. The risk of the severity of the disease in the cancer patients with COVID-19/SARS-CoV-2 infection is 45.4% (95% CI: 37.4–53.3). The Leave-one-out
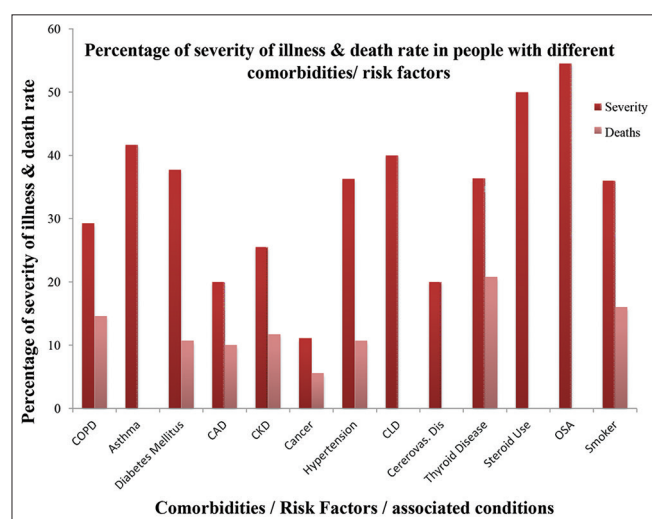
analysis showed risk estimates, which ranged from 43.1 to 47.9% upon removal of individual studies. Comparative analysis using four studies showed that cancer patients had a significantly higher risk of severe/critical disease (OR = 3.91; 95% CI: 2.70–5.67; *P* < 0.00001; *n* = 3845) as compared to non-cancer patients. The combined studies were homogenous (*P* = 0.18).

Cho SI *et al.*[21] found that after age and sex adjustment, hypertension, Type 2 diabetes mellitus, congestive heart failure (CHF), dementia, chronic pulmonary disease, liver diseases, renal diseases and cancer were significant risk factors for mortality.

Implications of available data for primary care physicians

Older age and associated comorbidities like diabetes mellitus, hypertension, thyroid disease, OSA syndrome and risk factors like smoking could help the clinicians to identify at an early stage those patients with COVID-19 who are at a higher risk for developing severe SARS-COV-2 disease and further help the physicians in better monitoring and management of the disease.

Conclusion

The age, gender and comorbidity disparities observed in COVID-19 vulnerability emphasise the need to understand the impact of age, gender and comorbidity on the incidence and case fatality of the disease and to tailor the treatment according to sex and gender. Experiences from the past outbreaks and pandemics have clearly shown the importance of incorporating age, gender and comorbidity analysis into the preparedness and response efforts of health interventions. The policies and public health efforts, however, have not yet addressed the age, gender and comorbidity impacts on disease epidemics, outbreaks or pandemics. Some countries have not disaggregated data by age, gender and comorbidity the way other countries have. In conclusion, the governments in all the countries should disaggregate and analyse data for age, gender and comorbidity differences. Furthermore, as prophylactic and therapeutic treatment studies begin, inclusion of age, gender and comorbidity analyses in their protocols must occur.

Summary

1. With advanced age, the severity of the illness and mortality rate was found to be increasing in patients.
2. Gender was not found to be an independent predictor of the severity of illness and mortality rate.
3. In patients suffering from diabetes mellitus, hypertension, thyroid disease, OSA and smokers, the severity of illness and mortality rate was found to be significant.

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Conflicts of interest
There are no conflicts of interest.

Figure 3: Percentage of severity of illness and death rate in people with different comorbidities/risk factors

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