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Sex-adjusted approach to baseline variables demonstrated some improved predictive capabilities for disease severity and survival in patients with Coronavirus Disease 19

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ABSTRACT

Introduction.

The study was focused on comparing crude and sex-adjusted hazard ratio calculated by the baseline variables which may have contributed to the severity of the disease course and fatal outcomes in Coronavirus Disease-19 (COVID-19) patients.

Method.

The study enrolled 150 eligible adult patients with confirmed SARS-CoV-2 infection. There were 61 (40.7%) male patients, and 89 (59.3%) female patients. Baseline information of patients was collected from patient medical records and surveys that the patients had completed on admission to the hospital.

Results.

Considerable number of baseline variables stratified according to disease severity and outcomes showed different optimal cut-points (OCP) in men and women. Sex-adjusted baseline data categories such as age; BMI; systolic and diastolic blood pressure; peripheral RBC and platelet counts; haematocrit; percentage of neutrophils, lymphocytes, monocytes, and their ratio; percentage of eosinophils; titre of plasma IL-6, IL-8, IL-10, and IL-17; and CXCL10; and ratio of pro- and anti-inflammatory cytokines demonstrated significant impacts on the development of the severe stage and fatal outcomes by the mean hazard ratio in the Kaplan-Meier and Cox regression models.

Conclusion.

This study confirmed some improved predictive capabilities of the sex-adjusted approach in the analysis of the baseline predictive variables for severity and outcome of the COVID-19.

1. Introduction

The COVID-19 pandemic continues to be an extraordinary event that has adversely affected the health of populations worldwide, posing a risk of international spread and interference with traffic-requiring coordinated international response [1]. Mongolia did not have an incidence of COVID-19 until November 10, 2020 despite the long border shared with China. Contagion was minimal due to early interventions approved by the WHO to delay the onset of the outbreak and its severity [2]. The country experienced four waves of the pandemic since the local spread of the infection. In Mongolia, from January 3, 2020 to May 24, 2022, a total of 922,628 confirmed cases of COVID-19 resulting in 2115 deaths have been reported to the WHO [3].

COVID-19 exerted much pressure on hospitals and health facilities. Clinical decision support systems based on predictive models helped to effectively improve the management of the pandemic [4]. One of the key

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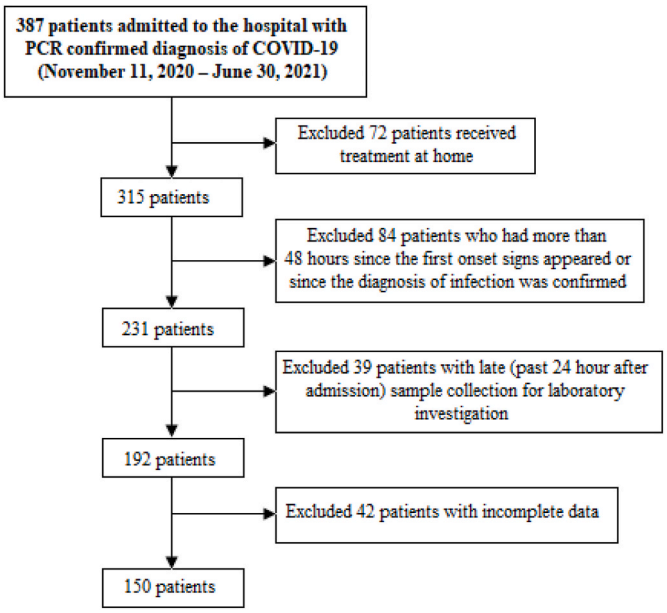

Fig. 1. Patient selection and eligibility flow chart.

measures taken to decrease the fatality rate was to strengthen early screening of severe COVID-19 patients and provide timely medical treatment [5]. COVID-19 typically manifests as a respiratory pathology, with a wide range of severity and clinical presentations. A spectrum of demographic, comorbidity, pulmonary function, and peripheral blood markers were reported to demonstrate a significant predictive ability for severe disease and fatal outcome [6–9]. The broad dysregulation of the innate immune system coupled with altered inflammatory responses expressed by the cytokine storm, and impaired adaptive immunity characterising the severe disease are more clearly reflected in the level of the inflammatory cytokines, present early information about the development of complications, and reflect important pathogenetic points [10,11].

Sex is a biological variable that affects the functions of the immune system [12]. Sex chromosome genes and sex hormones contribute to the differential regulation of immune responses between the sexes [12,13]. The impact of sex on the disease course and mortality of COVID-19 pandemics has not been fully clarified. Several systematic reviews and meta-analyses found a significant association between COVID-19 mortality and males [7,14]. Perhaps women are less likely to die from COVID-19; however, once a severe case of the disease occurs, the risk of a woman dying is similar to that of men [15].

In this study, we analysed demographic, biometric, seasonal, clinical, comorbidities, haematological, and immunological variables regarding a patient's sex and compared it with untreated variables. Our findings may be useful to the need of valuable and accurate predictive values for healthcare professionals working in resource-limited middle-level hospitals in Mongolia.

2. Methods

2.1. Study design and patients

In this prospective study, 150 adult patients were enrolled with confirmed SARS-CoV-2 infection and treated them in the Infectious Diseases Clinic of the National Centre for Communicable Diseases. These patients were selected from 387 patients who were being observed by physicians-members of the research team from October 11, 2020 to June 30, 2021. Patient selection and the categories of patients who were not considered eligible for the study are shown in Fig. 1.

Table 1
Distribution of baseline variables among patients with different disease severity and outcome*.

	All patients	Male patients	Female patients
Distribution of variables among patients developed severe disease			
Age >50 years	43 of 69 (62.3%), $p < 0.001$	18 of 28 (64.3%), $p > 0.05$	25 of 41 (61.0%), $p < 0.005$
Age >55 years	37 of 53 (69.8%), $p < 0.001$	17 of 23 (73.9%), $p < 0.01$	20 of 30 (66.7%), $p < 0.005$
Age >60 years	34 of 45 (75.6%), $p < 0.001$	15 of 20 (75.0%), $p < 0.05$	19 of 25 (76.0), $p < 0.001$
Age >65 years	25 of 33 (75.8%), $p < 0.001$	12 of 14 (85.7%), $p < 0.01$	13 of 19 (68.4%), $p < 0.05$
Age >70 years	22 of 30 (73.3%), $p < 0.005$	12 of 14 (85.7%), $p < 0.01$	10 of 16 (62.5%), $p > 0.05$
Obesity, BMI ≥≥ 30.0 kg/m^2	34 of 45 (75.6%), $p < 0.001$	8 of 12 (66.7%), $p > 0.05$	26 of 33 (78.8%), $p < 0.001$
Urban	69 of 129 (53.5%), $p < 0.001$	31 of 51 (60.8%), $p < 0.001$	38 of 78 (48.7%), $p < 0.05$
Admitted in spring season	54 of 72 (75.0%), $p < 0.001$	28 of 34 (82.4%), $p < 0.001$	26 of 38 (68.4%), $p < 0.001$
Multiple (3–5) onset sign	16 of 19 (84.2%), $p > 0.001$	6 of 6 (80.0%), $p > 0.01$	10 of 13 (76.9%), $p < 0.01$
Dry cough	54 of 78 (69.2%), $p < 0.001$	23 of 29 (79.3%), $p < 0.001$	31 of 49 (63.3%), $p < 0.001$
Shortness of breath	17 of 18 (94.4%), $p < 0.001$	6 of 6 (100.0%), $p < 0.05$	11 of 12 (91.7%), $p < 0.001$
Diarrhoea	9 of 12 (75.0%), $p > 0.05$	2 of 3 (66.7%), $p > 0.05$	7 of 9 (77.8%), $p < 0.05$
With coexisting disease	34 of 50 (68.0%), $p < 0.001$	15 of 20 (75.0), $p < 0.05$	19 of 30 (63.3%), $p < 0.05$
With multiple (2 or more) coexisting disease	16 of 19 (84.2%), $p < 0.001$	6 of 6 (100.0%), $p < 0.01$	10 of 13 (76.9%), $p < 0.05$
With coexisting CVD	10 of 13 (76.9%), $p < 0.05$	5 of 6 (83.3%), $p > 0.05$	5 of 7 (71.4%), $p > 0.05$
With coexisting PD	5 of 5 (100.0%), $p < 0.01$	3 of 3 (100.0%), $p > 0.05$	2 of 2 (100.0), $p > 0.05$
With coexisting AHT	18 of 27 (66.7%), $p < 0.05$	9 of 11 (81.8%), $p < 0.05$	9 of 16 (56.3%), $p > 0.05$
Abnormal breathing	13 of 16 (81.3%), $p < 0.01$	3 of 3 (100.0%), $p > 0.05$	10 of 13 (76.9%), $p < 0.05$
Distribution of variables among patients with fatal outcome of disease			
Age >50 years	13 of 69 (18.8%), $p < 0.001$	5 of 28 (17.9%), $p < 0.05$	8 of 41 (19.5%), $p < 0.05$
Age >55 years	13 of 53 (24.5%), $p < 0.001$	5 of 23 (21.7%), $p < 0.01$	8 of 30 (26.7%), $p < 0.005$
Age >60 years	12 of 45 (26.7%), $p < 0.001$	4 of 20 (20.0%), $p < 0.05$	8 of 25 (32.0%), $p < 0.001$
Age >65 years	11 of 33 (33.3%), $p < 0.001$	4 of 14 (28.6%), $p < 0.05$	7 of 19 (36.8%), $p < 0.001$
Age >70 years	10 of 30 (33.3%), $p < 0.001$	4 of 14 (28.6%), $p < 0.01$	6 of 16 (37.5%), $p < 0.005$
Admitted in spring season	13 of 72 (18.1%), $p < 0.001$	4 of 34 (11.8%), $p > 0.05$	9 of 38 (10.1%), $p < 0.001$
Multiple (3–5) onset sign	14 of 92 (15.2%), $p < 0.005$	5 of 34 (14.7%), $p > 0.05$	9 of 58 (15.5%), $p < 0.05$
Dry cough	13 of 78 (16.7%), $p < 0.005$	5 of 29 (17.2%), $p < 0.05$	8 of 49 (16.3%), $p < 0.05$
Diarrhoea	4 of 12 (33.3%), $p < 0.05$	0 of 3 (0%), $p > 0.05$	4 of 9 (44.4%), $p < 0.005$
With coexisting disease	9 of 50 (18.0%), $p < 0.05$	4 of 20 (20.0%), $p < 0.05$	5 of 30 (16.7%), $p > 0.05$
With coexisting AHT			

(continued on next page)

Table 1 (*continued*)

	All patients	Male patients	Female patients
Abnormal breathing	6 of 27 (22.2%), $p < 0.05$ 5 of 16 (31.3%), $p < 0.01$	2 of 11 (18.2%), $p > 0.05$ 1 of 3 (33.3%), $p > 0.05$	4 of 16 (25.0%), $p > 0.05$ 4 of 13 (30.8%), $p < 0.05$

Abbreviations: CVD, cardiovascular diseases; PD, pulmonary diseases; AHT, arterial hypertension.
Notes: *-shown only significant variables.

2.2. Disease severity and mortality

The severity of COVID-19 during the disease course was established according to the WHO "Clinical management of COVID-19. Interim Guidance" from May 17, 2020 [16] and "COVID-19. Clinical management. Living Guidance" from January 25, 2021 [17]. A total of 47 (31·3%) of patients were diagnosed with a mild stage of COVID-19, 33 (22·0%) with moderate stage, 54 (36·0%) with severe stage, and 16 (10·7%) were considered at the critical stage. Fourteen (9·3%) resulted in COVID-19-related deaths.

2.3. Data collection

Sociodemographic, biometric, and seasonal information of patients was collected from patient medical records and surveys that patients had completed on admission to the hospital. Data on the onset signs of SARS-CoV-2 infection and findings of physical examinations performed by physicians at admission to the hospital were collected from the medical records of patients. Data on coexisting diseases with COVID-19 were obtained from the same surveys and in-hospital observations.

2.4. Laboratory investigation

Peripheral blood samples were collected within 24 h after hospital admission. The red blood cell (RBC) count, white blood cell (WBC) count, platelet count, white blood cell differentials, and other haematological features were measured using a Sysmex XN-550 automated haematology analyser (Sysmex Co. Japan). The neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-neutrophil ratio (MNR) were calculated by dividing the corresponding values.

Blood samples for the cytokine study were collected separately within 24 h after patient admission to the hospital. Plasma cytokine and chemokine levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (Sunlong Biotech, China).

2.5. Patient and public involvement

Research was carried out with active participation and volunteering of patients in observational study.

2.6. Statistical analysis

Data was analysed using descriptive and analytical statistics. Distribution of nominal or ordinal variables of severity or survival clusters was compared using Pearson's Chi-square test. Distribution of nominal or ordinal baseline variables among severe and non-severe cases, deaths and recovered patients was compared using Fisher's exact test in all patients. Then male and female patients were analysed separately. Continuous quantitative variables such as age, BMI, findings of examination at admission to the hospital, and laboratory findings were analysed using receiver operating characteristics (ROC) analysis which was divided into categories according to the following steps. First, ROC curves stratified by disease severity (mild and moderate vs. severe) and survival (died vs. recovered) were constructed separately for all male and female. Second, the optimal cut-off point (OCP) was determined by corresponding the maximum value of the Youden index. Patients were divided into comparable categorical clusters using OCP (non-severe vs. severe and recovered vs. died). Hazard and survival functions during the disease course were analysed using Kaplan-Meier survival analysis, and statistical significances were evaluated using the Mantel-Cox test. Hazard ratios (HRs) calculated by using Cox regression analysis. Statistical significance was expressed using p values of <0·05, <0·01, <0·005, and <0·001.

3. Results

3.1. Disease severity and mortality

Seventy (46·7%) patients were diagnosed with severe COVID-19. Of which, 58 (82·9%) patients were diagnosed during their hospital admission (day 0). Progression of the disease from mild and moderate stages into severe stage was observed in 12 (17·1%) patients, including 4 (5·7%) patients whose severity progressed on day 1 after admission, 7 (10·0%) patients on day 2, and 1 (1·4%) on day 3.

Fatal outcomes of COVID-19 were observed in 14 (9·4%) of 150 patients. Deaths (7.1%) occurred on days 3, 5, 7, 10, 17, 20, 23, 27, and 30 after admission to the hospital, resulting in 9 (64·3%) fatal cases. Two deaths (14·3%) occurred on day 14, and three deaths (21·4%) occurred 24 days after admission to the hospital.

3.2. Baseline data of patients and its association with disease severity and outcome

Distribution of sociodemographic variables, such as age range, permanent place of residence, and employment status, were found to be significantly different according to disease stage and outcome of COVID-19 (Pearson's Chi-square; $p < 0.05$). The mean value and median of the quantitative biometric variables, such as age and body mass index (BMI), varied significantly according to disease stage (Supplementary Table 1) and outcomes (Supplementary Table 2). The body habitus of patients was associated with disease severity but not with disease outcome. The season in which the patient was infected with SARS-CoV-2 and hospitalised for treatment demonstrated a strong association with the percentage of severe disease and fatal outcome.

Distribution of some baseline clinical parameters was significantly different among patients with different disease severities (Supplementary Table 3) and outcomes (Supplementary Table 4). Patients with severe disease and fatal outcomes demonstrated a higher count of multiple onset signs of disease and a higher count of multiple coexisting diseases. Manifestation of the disease with dry cough, shortness of breath, difficulty breathing, and diarrhoea was associated with a severe course of the disease and fatal outcomes. The coexistence of arterial hypertension, cardiovascular, and pulmonary diseases were also associated with the severity of the disease's course and outcome. The mean values of physical examination findings at the time of admission to the hospital, including breath and pulse per minute, systolic and diastolic blood pressure, and oxygen saturation rate, were associated with disease severity and outcome. Abnormal breathing was observed more often in patients with severe disease and fatal outcomes.

Mean values of platelet count, percent and ratio of white blood cell differentials (percent of neutrophil, lymphocyte, monocyte, eosinophil, basophil, and NLR and MNR), plasma cytokines and chemokine (titre of IL-8 and IL-6) were associated with disease severity. No significant difference in titre of plasma IL-10, IL-17, and CXCL10 was found; however, ratios of cytokines and chemokines (IL-6/IL-10, IL-8/IL-10, CXCL10/IL-8, CXCL10/IL-10, and IL17/IL-8) were associated with disease severity (Supplementary Table 5). Patients with fatal outcomes demonstrated significantly increased mean value of WBC, neutrophil percent, and NLR, but their mean value of RBC, haematocrit, lymphocyte percentage, monocyte percentage, and MNR were significantly lower than those of recovered patients. IL-17/IL-8 ratio and CXCL10/IL-8 ratio was

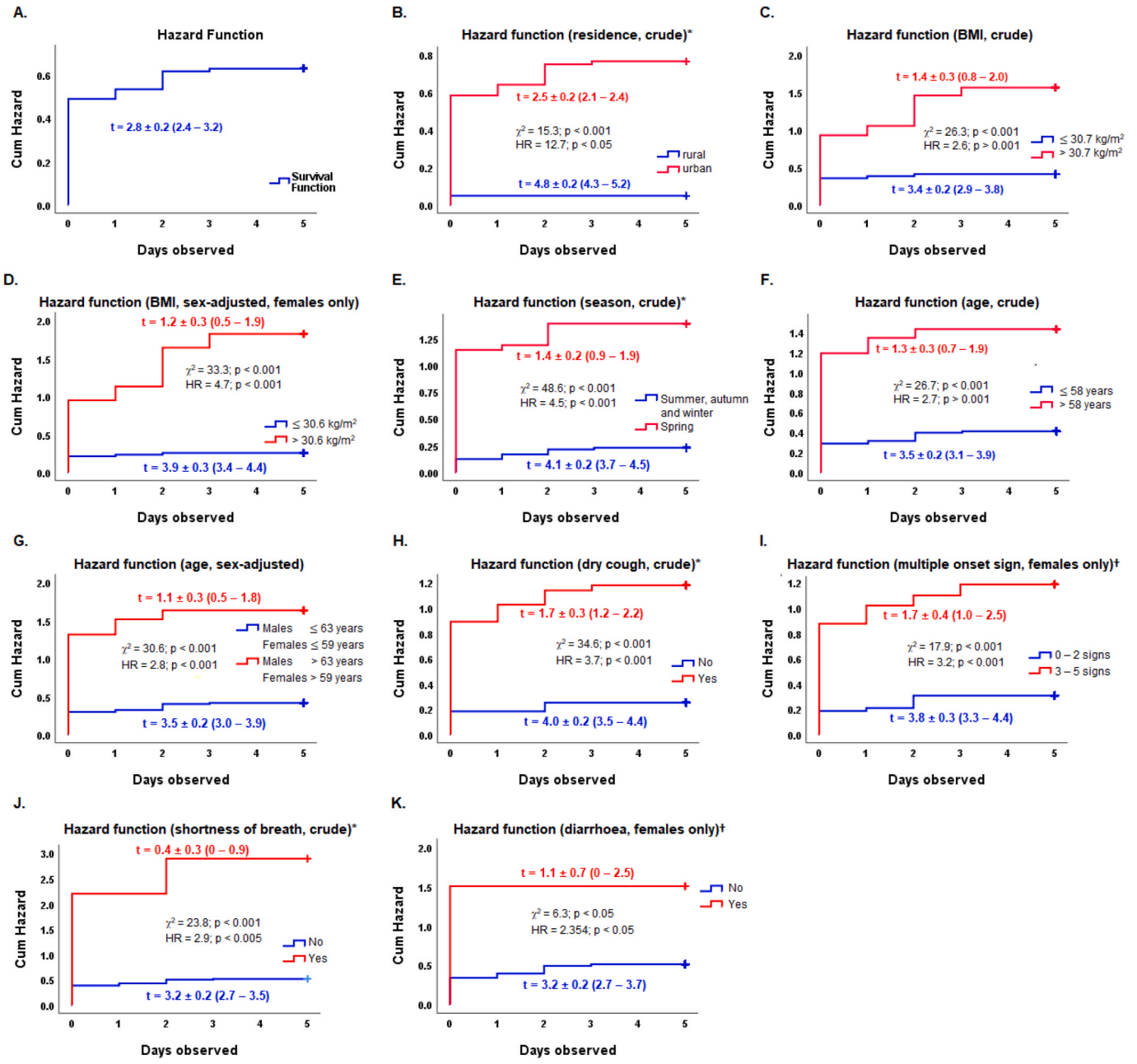

Figure 2. Hazard functions for progression into severe stage of the COVID-19 according to sociodemographic, biometric, seasonal, and onset sign variables. A. General hazard function of progression into a severe stage of COVID-19; B. Hazard functions of progression into a severe stage in urban and rural residents; C. Hazard functions of progression into a severe stage arranged by crude BMI; D. Hazard functions of progression into a severe stage arranged by sex-adjusted BMI; E. Hazard functions of progression into a severe stage in patients admitted to the hospital in different seasons of the year; F. Hazard function of progression into a severe stage in patients stratified by the crude age strata; G. Hazard function of progression into a severe stage in patients stratified by the sex-adjusted age strata; H. Hazard function of progression into a severe stage in patients with onset dry cough; I. Hazard function of progression into a severe stage in female patients with multiple onset signs; J. Hazard function of progression into a severe stage in patients with onset shortness of breath (difficulty breathing); K. Hazard function of progression into a severe stage in patients with onset diarrhoea. t, mean time for progression into a severe stage (days); χ^2, chi-square (Mantel-Cox test); HR, hazard ratio (Cox regression); BMI, body mass index. Notes: *-hazard ratio of the sex-adjusted variable found same as the crude variable; †-HR for the crude variable was not significant.

significantly higher in patients with fatal outcome compared to recovered patients (Supplementary Table 6).

3.3. Sex adjustment and clustering of baseline variables

Patients with clinical stages ranging from mild to moderate and from severe to critical were categorised into non-severe and severe clusters for hazard and survival analysis. Distribution of nominal or ordinal baseline variables were calculated among the severe and non-severe cases, deaths and recovered patients within three separate groups: all patients, males and females. Variables demonstrated significant distribution in these groups are presented in Table 1.

OCPs were calculated for quantitative baseline variables using ROC analysis, and the variables were stratified according to severity and outcome. Baseline variables of severe patients were compared with baseline variables of non-severe cases. Age; BMI; systolic and diastolic

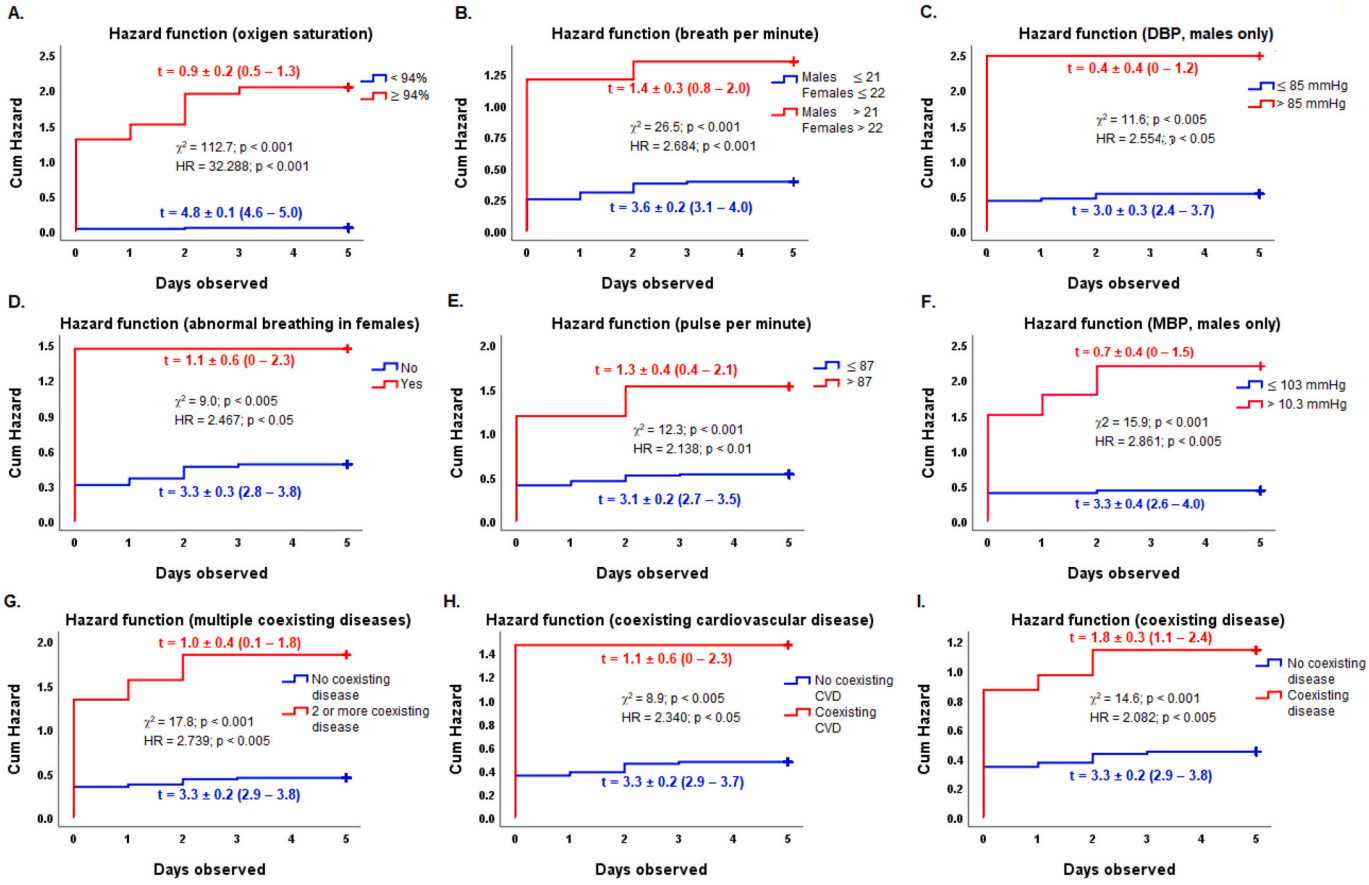

Figure 3. Gender adjusted hazard functions for progression into severe stage of the COVID-19 according to findings at admission to hospital and coexisting diseases. A. Hazard function of progression into a severe stage stratified by oxygen saturation rate; B. Hazard function of progression into a severe stage in patients stratified by the breath count per minute; C. Hazard function of progression into a severe stage in male patients stratified by diastolic blood pressure; D. Hazard function of progression into a severe stage in female patients stratified by presence of abnormal breath; E. Hazard function of progression into a severe stage in female patients stratified by pulse count per minute; F. Hazard function of progression into a severe stage in male patients stratified by median blood pressure; G. Hazard function of progression into a severe stage stratified by presence of 2 or more coexisting diseases; H. Hazard function of progression into a severe stage stratified by presence of coexisting cardiovascular disease; I. Hazard function of progression into a severe stage stratified by presence of a coexisting disease. t, mean time for progression into severe stage (days); χ^2, chi-square (Mantel-Cox test); HR, hazard ratio (Cox regression); DBP, diastolic blood pressure; MBP, median blood pressure; mmHg, millimetre of mercury; CVD, cardiovascular disease

blood pressure (SBP and DBP, respectively) measured at time of admission to the hospital; peripheral RBC and platelet counts; haematocrit; percentage of neutrophils, lymphocytes, monocytes, and their ratio; percentage of eosinophils; titre of plasma IL-6, IL-8, IL-10, and IL-17; titre of plasma chemokine CXCL10; and ratio of pro- and anti-inflammatory cytokines stratified by disease severity showed different OCPs in male and female patients. Some variables, namely breath and pulse count, oxygen saturation rate, and plasma IL-8 stratified by disease severity, showed the same OCP in male and female patients (Supplementary Figs. 1–9). Using the same approach, OCPs were calculated using baseline quantitative variables for patients who survived and died. Age, breathing rates, systolic blood pressure, and oxygen saturation rate measured at time of admission; peripheral RBC; haematocrit; percentage of neutrophils, lymphocytes, monocytes, and their ratio; percentage of eosinophils; titre of plasma IL-8; titre of plasma chemokine CXCL10; and ratio of pro- and anti-inflammatory cytokines stratified by disease outcomes showed different OCPs in male and female patients (Supplementary Figs. 10–15).

These calculations allowed classification of the patients into two groups according to distribution of baseline variables for further hazard and survival analysis, while OCP values were included into the low-risk group.

Hazard ratio for development of severe stages of COVID-19 and covid-related death according to baseline variables.

The hazard function was analysed for the development of severe diseases within the first five days of admission (Fig. 2A). Crude and sex-adjusted categories of baseline variables were compared as a risk factor using the Kaplan-Meier hazard function (χ^2, Mantel Cox test). Crude and sex-adjusted hazard functions by baseline variable category are presented in Figs. 2–5.

The survival function of patients within 32 days of admission to the hospital is presented in Fig. 6A. Comparative analysis of crude and sex-adjusted baseline variable categories with significant impact on survival of patients during the disease course was performed using the Kaplan-Meier and Cox regression model (Figures 6, 7).

Comparison of sex-adjusted HR values with crude HRs (Table 2) demonstrated some principal qualitive and quantitative differences between these values. We calculated HR ratios for severe diseases in 33 variables, and 6 of them demonstrated not significant crude HR, 4 variables demonstrated significant HR for female patients, another 4 were significant only in male patients. Then we calculated HR ratios for fatal outcome in 14 variables, and 4 of them demonstrated not significant crude HR, and 7 variables demonstrated significant HR only for female patients.

4. Discussion

Baseline data related risks of severe disease and death have been well

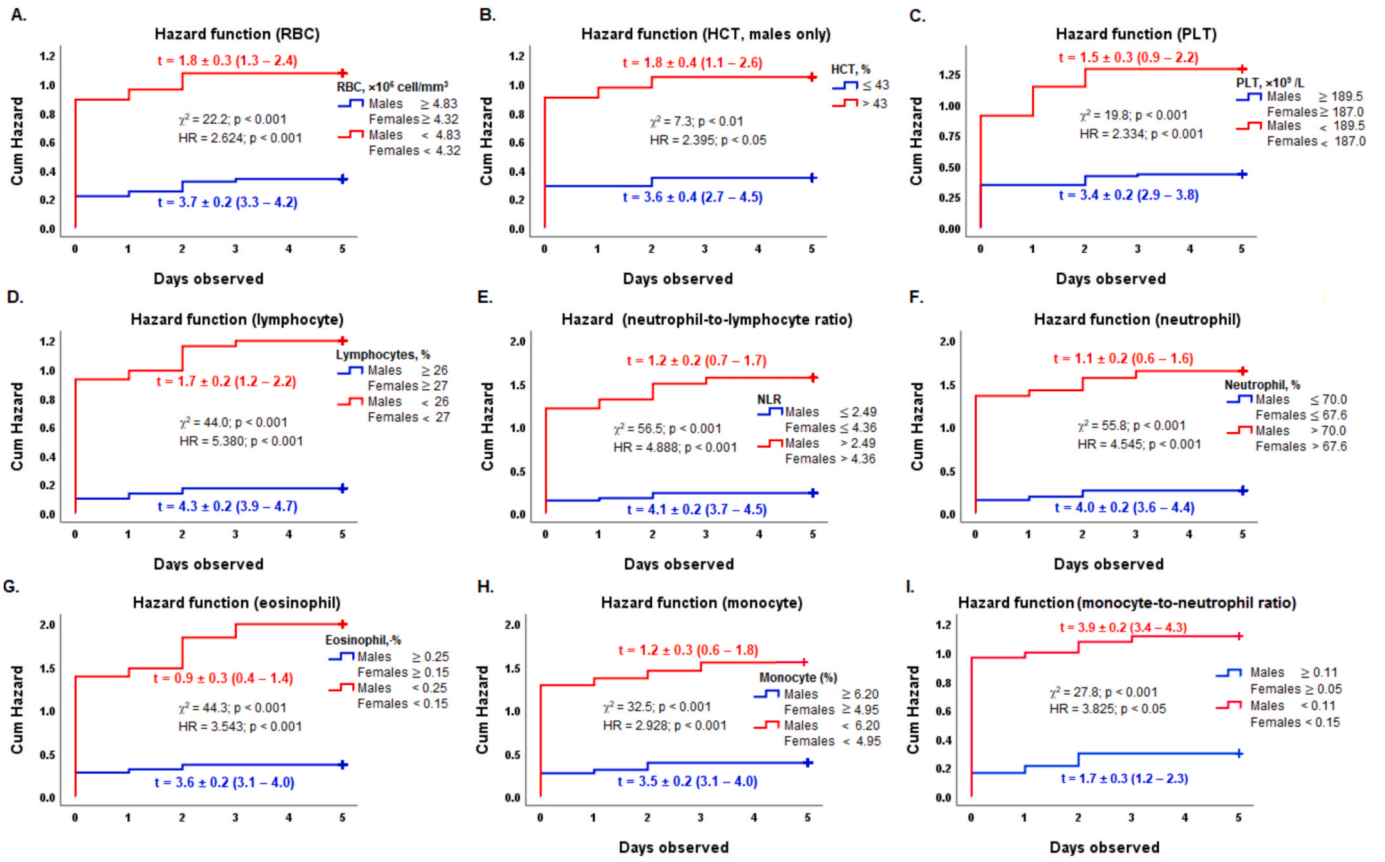

Figure 4. Gender adjusted hazard functions for progression into severe stage of the COVID-19 according to haematological variables. A. Hazard function of progression into a severe stage stratified by count of red blood cells; B. Hazard function of progression into a severe stage in male patients stratified by haematocrit; C. Hazard function of progression into a severe stage stratified by platelet count; D. Hazard function of progression into a severe stage stratified by lymphocyte percent; E. Hazard function of progression into a severe stage stratified by neutrophil-to-lymphocyte ratio; F. Hazard function of progression into a severe stage stratified by neutrophil percent; G. Hazard function of progression into a severe stage stratified by eosinophil percent; H. Hazard function of progression into a severe stage in male patients stratified by monocytes percent; I. Hazard function of progression into a severe stage in male patients stratified by monocytes-to-neutrophil ratio. χ^2, chi-square (Mantel-Cox test); HR, hazard ratio (Cox regression); RBC, red blood cell; HCT, haematocrit; PLT, platelet; NLR, neutrophil-to-lymphocyte; MNR, monocytes-to-neutrophil

documented–including the number of meta-analyses. There were reports of a significant association between patients age and gender [7,9,18–20]; obesity [19,21,22]; respiratory [23–25], circulatory [26–28] and gastrointestinal [29] onset signs and baseline clinical manifestation; baseline haemotological variations [30–33]; and cytokine profile [8,10,11,34–40]. Crude data we found coincides with these findings and risk factors were in the spectrum of estimated risk factors previously reported. However, none of these studies reported risk factors calculated separately in men and women.

Principle findings of the study can be summarized as follows: i) quantitative baseline variables in male and female patients with SARS-CoV-2 infection demonstrated different optimal cut-points by ROC analysis depending on the severity of diseases course and outcome. Therefore, using these cut-points, sex-adjustments of variables and patients can be classified into clusters according to risk of severity of the disease or fatal outcome; ii) sex-adjusted hazard ratio demonstrated considerable number of qualitive and quantitative differences compared to crude variables in Kaplan-Meier and Cox regression survival model. Actually, comprehensive explanations or credible hypotheses to each of these differences cannot be provided. However, sex does have considerable impact on immune function and plays an important role in development of immune disorder pathologies including autoimmune, and autoinflammatory diseases [41]. Sex chromosome genes and sex hormones, including estrogens, progesterone and androgens, contribute to the differential regulation of immune responses between the sexes [12,13,42]. It was hypothesized that females are better protected against systemic inflammation-induced endothelial dysfunction. This effect is likely due to accelerated resolution of inflammation compared with males, specifically via neutrophils, mediated by an elevation of the D-resolvin pathway [43]. Fernández-de-las-Peñas et al. (2022) suggested that the female sex has a risk factor for the development of some long-term post-COVID symptoms, including mood disorders [44]. Raimondi et al. (2021) concluded that hospitalised women are less likely to die from COVID-19; however, once a severe disease occurs, the risk of dying is similar to that in men [15]. However, strong evidence for a sex-based difference in mortality for COVID-19 was lacking [45]. Sex-related risks of severe disease and death have been well documented, including the number of meta-analyses [7,9,20]. However, a search in related literature source using the keywords “sex-adjusted hazard ratio, severity and mortality, COVID-19″ did not result in any findings or similar reports.

Two interesting findings were discovered. First, the percentage of residents of Ulaanbaatar City and its suburban area among patients who developed severe disease was found to be significantly higher than that of rural residents. Ulaanbaatar, the coldest capital city in the world, is home to half of Mongolia’s population, much of which uses coal for household heating, contributing to high wintertime air pollution [46]. The air quality in Ulaanbaatar has been reported to be much lower in winter than in rural areas and the impact of air pollution on cardiovascular and respiratory diseases of urban residents has been reported [47]. Based on the above-mentioned circumstances, it is assumed that air pollution in Ulaanbaatar may be one possible explanation for the

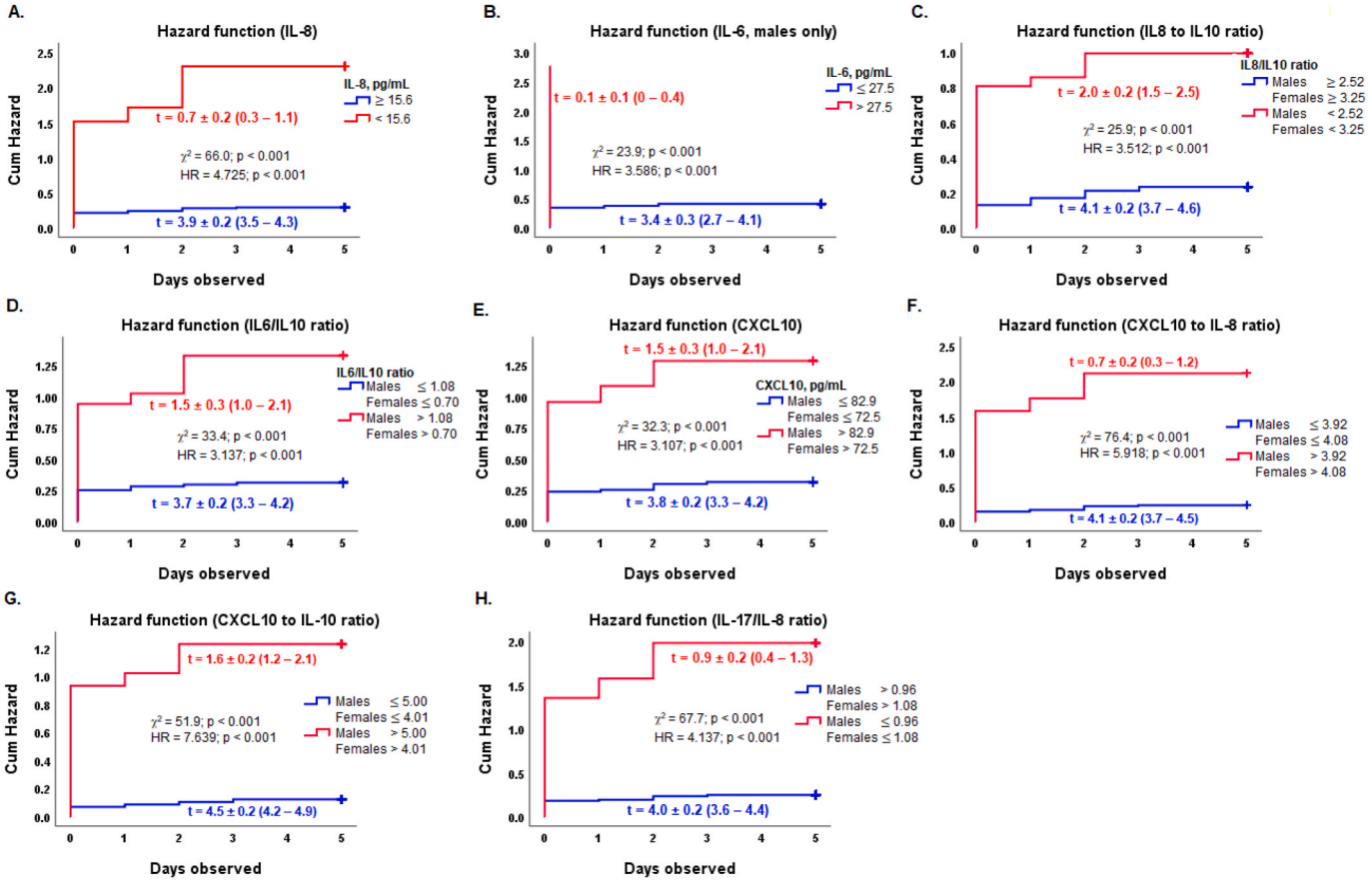

Figure 5. Gender adjusted hazard functions for progression into severe stage of the COVID-19 according to immunological variables. A. Hazard function of progression into a severe stage according to IL-8 titre; B. Hazard function of progression into a severe stage in male patients according to IL-8 titre; C. Hazard function of progression into a severe stage according to IL8/IL10 ratio; D. Hazard function of progression into a severe stage according to IL6/IL10 ratio; E. Hazard function of progression into a severe stage according to CXCL10 titre; F. Hazard function of progression into a severe stage according to CXCL10 to IL-8 ratio; G. Hazard function of progression into a severe stage according to CXCL10 to IL10 ratio; H. Hazard function of progression into a severe stage according to IL-17 to IL-8 ratio χ^2, chi-square (Mantel-Cox test); HR, hazard ratio (Cox regression); IL, interleukin; pg, picogram; CXCL, C – X- C motif chemokine ligand

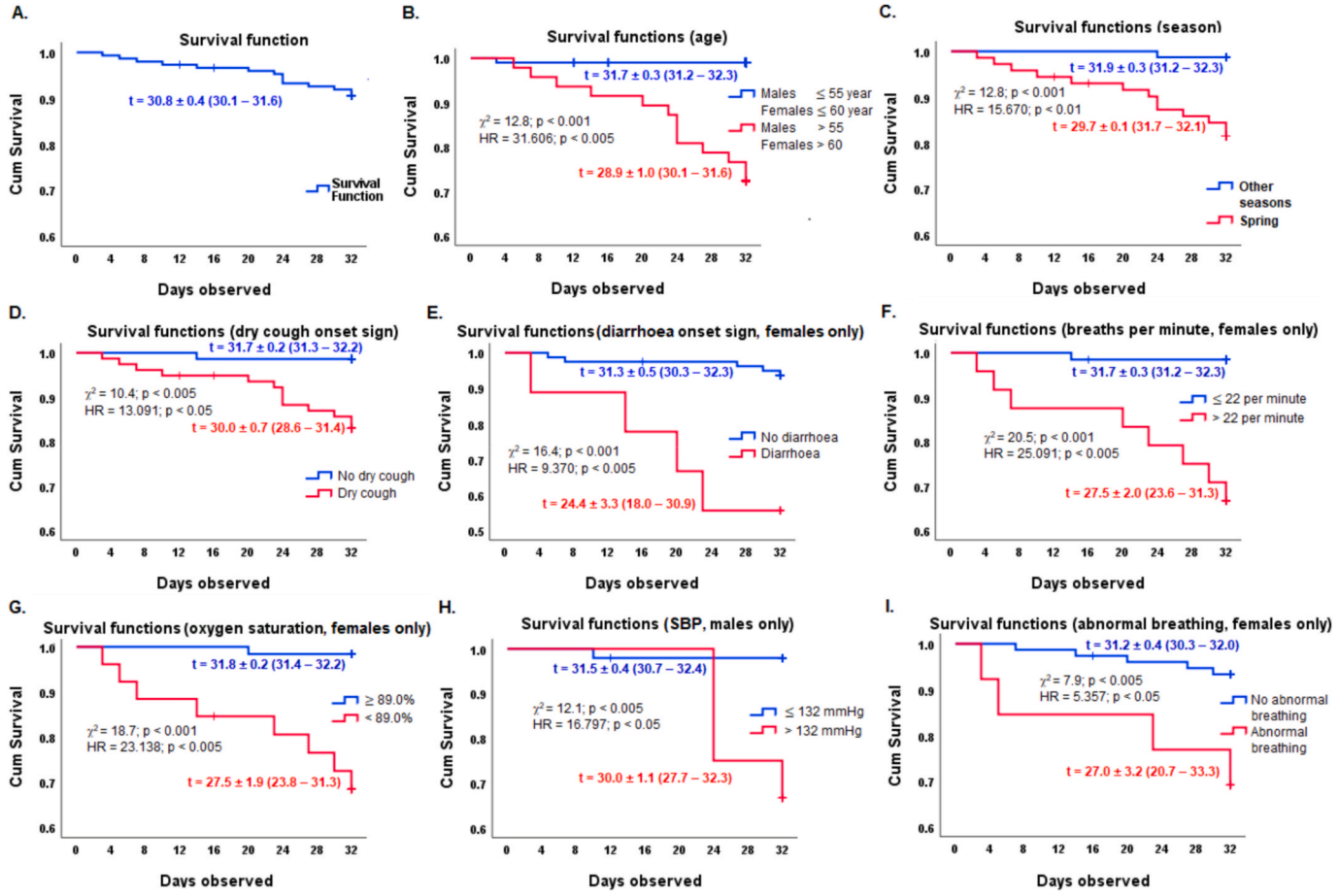

Figure 6. Gender adjusted Kaplan-Meier survival functions in patients with COVID-19 according to sociodemographic, seasonal, onset sign, and findings at admission to hospital variables. A. Kaplan-Meier survival functions in patients with COVID-19; B. Gender adjusted survival function according to patient's age; C. Survival function according to the season when patient admitted to the hospital; D. Survival function according to presence of dry cough onset sign; E. Gender adjusted survival function according to presence of diarrhoea onset sign in female patients; F. Gender adjusted survival function according to breath count per minute; G. Gender adjusted survival function according to oxygen saturation rate; H. Gender adjusted survival function according to systolic blood pressure; I. Gender adjusted survival function according to presence of abnormal breathing. t, mean time of progression into a severe stage and its 95% confidence interval (days); χ^2, chi-square (Mantel-Cox test); HR, hazard ratio (Cox regression); SBP, systolic blood pressure; mmHg, millimetre of mercury

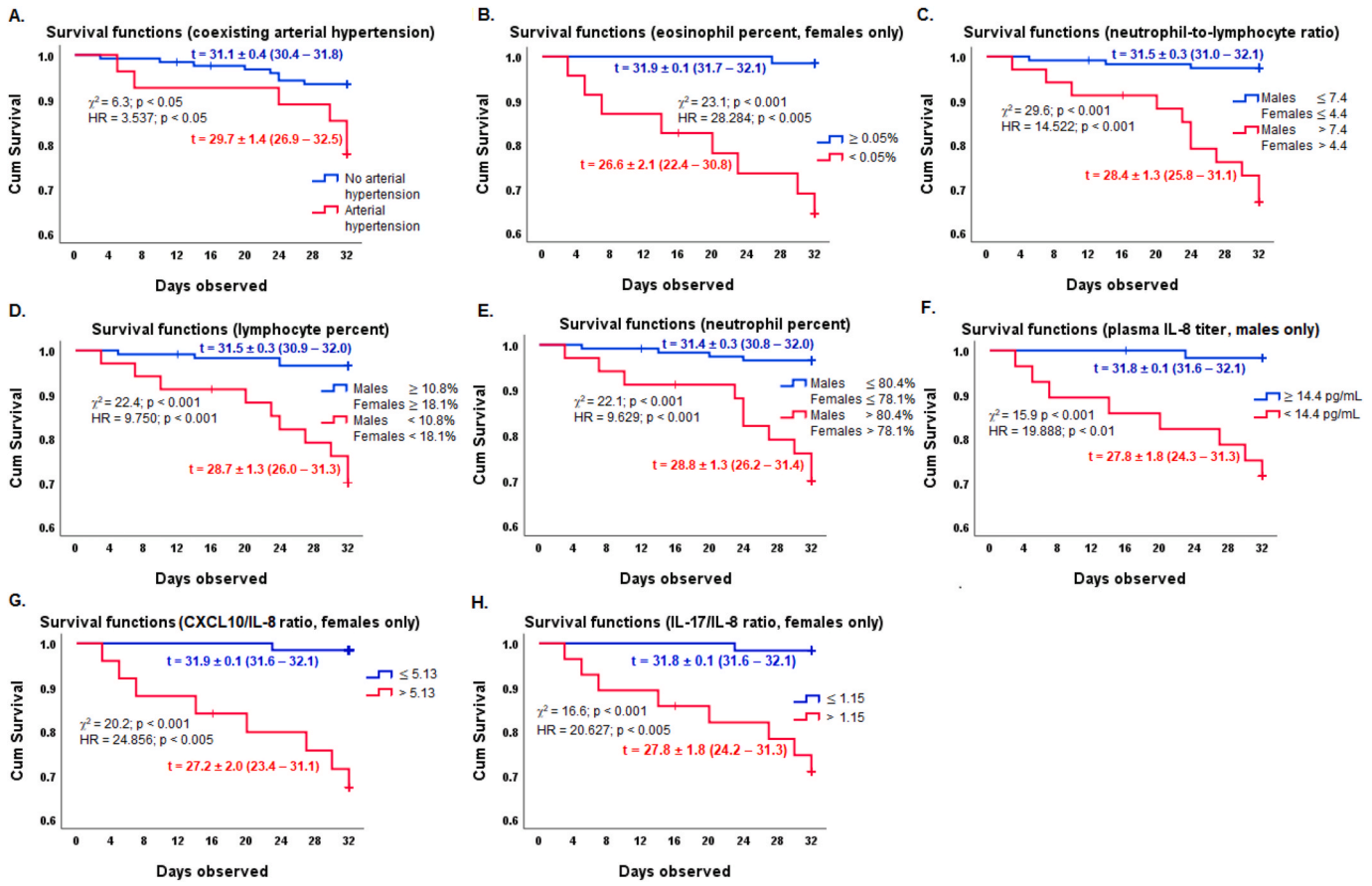

Figure 7. Gender adjusted Kaplan-Meier survival functions in patients with COVID-19 according to coexisting diseases, haematological and immunological variables. A. Kaplan-Meier survival functions according to coexisting arterial hypertension; B. Survival function according to eosinophil percent in female patients; C. Gender adjusted survival function according to neutrophil-to-lymphocyte ratio; D. Gender adjusted survival function according to lymphocyte percent; E. Gender adjusted survival function according to neutrophil percent; F. Gender adjusted survival function according to plasma IL-8 titre; G. Gender adjusted survival function according to plasma CXCL10 to IL-8 ratio; H. Gender adjusted survival function according to IL-17 to IL-8 ratio. t, mean time of progression into a severe stage and its 95% confidence interval (days); χ^2, chi-square (Mantel-Coxtest); HR, hazard ratio(Cox regression); IL, interleukin; pg/mL, picogram per millilitre; CXCL, C – X- C motif chemokine ligand

frequency of severe cases of COVID-19 increasing in the spring. Second, ratios of pro- and anti-inflammatory cytokines and chemokines have shown an excellent predictive ability and demonstrates information regarding the severity of the disease is no less important than the titres of the cytokines themselves. Predictive role of pro- and anti-inflammatory cytokines and chemokines for disease severity and mortality have been described very well [10,11,36,38,39,48]. However, very few studies are concerned with the ratio of these messenger molecules playing crucial role in inflammation [49].

The study was conducted during the pandemic and covered a limited number of clinical cases which should be confirmed in large clinical data. Nevertheless, findings have shown the need for a sex-specific approach for severe diseases demonstrating disorders of the immune function to which severe COVID-19 can be confidently counted. A considerable number of demographics, biometric, seasonal, clinical, comorbidity, hematological, immunological variables and covariates were found to be associated with higher risk of severe disease and adverse outcome of COVID-19. Sex-specific and differentiated cut-points of some baseline variables were established for predicting disease severity and outcome. Some important predicative variables were identified but these could not be confirmed by crude data. Hopefully, these findings will be used by frontline health professionals as a valuable and accurate predictive value for disease severity and outcomes in resource-limited middle level hospitals not only in Mongolia, but other developing countries.

5. Summary

This study demonstrated reasonability the sex-adjusted approach in analysis of the baseline predictive variables for severity and outcome of the COVID-19. Male and female patients showed different optimal cut-points in the number of continuous baseline variables and therefore different predictive classifications of the disease severity and outcome. Ratio of pro-inflammatory and anti-inflammatory cytokines and chemokines have shown a valuable predictive ability. Considerable number of baseline variables found associated with higher risk of severe disease and adverse outcome of COVID-19 in this study. Hopefully, these findings will be used as valuable and accurate predictive values in resource-limited middle level hospitals.

Data availability statement

The original contributions presented in the study are included in the Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical issues of the study were reviewed and approved in Ethical Review Committee under the Ministry of Health, resolution no. 172, from July 8, 2020.

Table 2
Comparison of crude and sex-adjusted hazard ratio*.

Variables	Crude HR			Sex-adjusted HR		
	Factor	HR (95% CI)	p	Factor	HR (95% CI)	p
A. Severe disease						
Age (years)	>58	2.7 (1.6–4.3)	<0.001	males >63; females >59	2.8 (1.8–4.6)	<0.001
Obesity (BMI, kg/m^2)	>30.7	2.6 (1.6–4.2)	<0.001	30.6 (females only)	4.7 (2.4–9.3)	<0.001
Residence	urban	12.7 (1.8–91.8)	<0.001	urban	12.7 (1.8–91.8)	<0.001
Admitted season	spring	4.5 (2.6–8.0)	<0.001	spring	4.5 (2.6–8.0)	<0.001
Multiple (3–5) onset signs	yes		>0.05	yes (females only)	3.2 (1.6–6.2)	<0.005
Dry cough onset sign	yes	3.7 (3.3–4.1)	<0.001	yes	3.7 (3.3–4.1)	<0.001
Shortness of breath onset sign			>0.05	yes		
Diarrhoea onset sign	yes		>0.05	yes (females only)	2.3 (1.0–5.4)	<0.05
Oxygen saturation	<94.0%	32.3 (4.1–355.6)	<0.001	<94.0%	32.3 (4.1–355.6)	<0.001
MBP (mmHg)			>0.05	>103.0 (males only)	2.9 (1.4–5.8)	<0.005
Breath per minutes	>21	3.2 (2.0–5.2)	<0.001	males >21; females >22	2.7 (1.7–4.3)	<0.001
DBP (mmHg)			>0.05	>85 (males only)	2.5 (1.2–5.4)	<0.05
Abnormal breath			>0.05	yes (females only)	2.5 (1.2–5.1)	<0.05
Pulse per minute	>87	2.1 (1.2–3.7)	<0.01	>87	2.1 (1.2–3.7)	<0.01
Multiple (≥2) coexisting disease	yes	2.7 (1.5–5.0)	<0.005	yes	2.7 (1.5–5.0)	<0.005
Coexisting CVD	yes	2.3 (1.2–4.7)	<0.05	yes	2.3 (1.2–4.7)	<0.05
Presence of coexisting disease	yes	2.1 (1.3–3.3)	<0.005	yes	2.1 (1.3–3.3)	<0.005
Lymphocyte (%)	<20.6	3.9 (2.3–6.6)	<0.001	males <26.0; females <27.0	5.4 (2.7–10.6)	<0.001
Neutrophil (%)	>67.6	4.5 (2.6–7.8)	<0.001	males >70.0; females >67.6	4.5 (2.7–7.7)	<0.001
NLR	>3.82	2.1 (1.6–2.7)	<0.001	males >2.49; females >4.36	4.9 (2.8–8.5)	<0.001
MNR	<0.09	2.8 (1.7–4.6)	<0.001	males <0.11; females <0.15	3.0 (1.8–5.2)	<0.001
Eosinophil (%)	<0.15	3.4 (2.1–5.4)	<0.001	males <0.25; females <0.15	3.5 (2.1–5.6)	<0.001
Monocyte (%)	<4.95	2.6 (1.6–4.3)	>0.001	males <6.20; females <4.95	2.9 (1.8–4.7)	<0.001
RBC (× 10^6 cell/mm^3)	<4.31	1.9 (1.2–3.1)	<0.01	males <4.83; females <4.32	2.624 (1.6–4.4)	<0.001
Hematocrit (%)	<39.5	1.8 (1.1–3.0)	<0.05	<43.0 (males only)	2.4 (1.0–5.6)	<0.05
Platelet (× 10^9/L)	<188.0	2.3 (1.4–3.6)	<0.005	males <189.5; females <187.0	2.3 (1.4–3.7)	<0.001
CXCL10/IL-10 ratio	>5.00	5.8 (2.9–11.4)	<0.001	males >5.00; females >4.01	7.6 (3.5–16.8)	<0.001
IL-17/IL-10 ratio	<1.61	3.2 (1.7–6.2)	<0.001	males >2.25; females >1.60	3.0 (1.7–5.2)	<0.01
IL-8 (pg/mL)	<15.6	4.7 (2.8–7.9)	<0.001	<15.6	4.7 (2.8–7.9)	<0.001
IL-6 (pg/mL)	>5.82	2.2 (1.3–3.8)	<0.005	>27.5 pg/mL (males only)	3.6 (1.7–7.4)	<0.005
IL-8/IL-10 ratio	<3.25	3.5 (1.7–7.1)	<0.001	males <2.52; females <3.25	3.5 (1.9–6.6)	<0.001
IL-6/IL-10 ratio	>0.70	3.2 (1.8–5.4)	<0.001	males >1.08; females >0.70	3.2 (1.9–5.2)	<0.001
CXCL10 (pg/mL)	>72.5	3.3 (2.0–5.5)	<0.001	males >82.9; females >72.5	3.1 (1.9–5.1)	<0.001
B. Survival						
Age (years)	>55	25.9 (3.4–198.3)	<0.005	males >55; females >60	31.6 (4.1–241.7)	<0.005
Season	spring	15.7 (2.0–119.8)	<0.01	spring	15.7 (2.0–119.8)	<0.01
Dry cough onset sign	yes	13.1 (1.7–100.1)	<0.05	yes	13.1 (1.7–100.1)	<0.05
Diarrhoea onset sign			>0.05	diarrhoea onset sign (females only)	9.4 (2.5–35.1)	<0.005
Breath per minutes	>22	12.1 (3.4–43.4)	<0.001	>22 (females only)	25.1 (3.1–200.8)	<0.005
Oxygen saturation			>0.05	<89% (females only)	23.1 (2.9–185.2)	<0.005
SBP (mmHg)			>0.05	>132 mmHg (females only)	16.8 (1.9–150.6)	<0.05
Abnormal breathing	yes	5.2 (1.7–15.6)	<0.005	yes (females only)	5.3 (1.4–20.0)	<0.05
Coexisting AHT	yes	3.5 (1.2–10.2)	<0.05	yes (females only)	3.9 (1.0–14.5)	<0.05
Eosinophil (%)	<0.05	12.3 (3.4–44.0)	<0.001	<0.05 (females only)	28.7 (3.6–230.1)	<0.005
NLR	>8.2	10.0 (3.5–29.0)	<0.001	males >7.9; females >4.4	14.5 (4.0–52.1)	<0.001
Lymphocyte (%)	<10.6	7.5 (2.0–27.9)	<0.001	males <10.8; females <18.1	9.7 (3.0–31.1)	<0.001
Neutrophil (%)	>78.6	8.2 (2.6–26.0)	<0.001	males >80.4; females >78.1	9.6 (3.0–30.7)	<0.001
IL-8 (pg/mL)			>0.05	<14.4 pg/mL (females only)	19.9 (2.5–159.1)	<0.01

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; MBP, median blood pressure; DBP, diastolic blood pressure; mmHg, millimeter of mercury; NLR, neutrophil-to-lymphocyte ratio; MNR, monocyte-to-neutrophil ratio; RBC, red blood cell; L, liter; CXCL, C-X-C motif chemokine ligand; IL, interleukin; pg/mL, picogram per millilitre; SBP, systolic blood pressure; AHT, arterial hypertension. Notes: *-shown only significant variables.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.imu.2022.100982.

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