INTRODUCTION
The SARS-CoV-2 epidemic started in late December 2019 in China; the virus has been first emerged in Wuhan. SARS-CoV-2 causes respiratory disease and pneumonia and so it is called Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2, and its related disease named Coronavirus Disease 2019, COVID-19. It is reported that SARS-CoV-2 shows a wide spectrum of the clinical consequences, including asymptomatic infection toward acute respiratory damage. The clinical symptoms of this infection have been observed heterogeneous but some are common at the onset of the disease; fever, dry cough, and shortness of breath. COVID-19 virus through S1 domain of spike protein on the virion, binds to the extracellular domain of Angiotensin converting enzyme (ACE2) in the cell membrane, then fusion of the viral and cell membranes occurs. Following that, viral RNA transfers its genome inside the cell; ultimately makes new virions that infects other cells. The receptor of ACE2 is almost present in the plasma membrane of all organs, including cardiovascular system. Its expression is reported in the endothelium of capillaries, vascular smooth muscles, coronary arteries, ventricular myocardium. Abnormal function of RAS is associated with the development of heart disease and hypertension. ACE inhibitors and angiotensin II receptor blockers (ARBs) are as routine drugs to treat some chronic diseases, like hypertension. It is reported that heart failure patients are prone to COVID-19 infection because of increased plasminogen level. Plasmin removes the extracellular domain of S-protein of the virus and elevates its affinity to bind with ACE2 and
facilitates virus entry to the host cells. It is documented that, patients with disease like hypertension, cardiovascular and kidney disease, showed severe clinical outcomes when infected with COVID-19. Some studies have reported men are more sensitive to COVID-19 than female and showed more mortality rate they may have more ACE2 receptor but Chen et al. reported that women are more protected against COVID-19 because of high tissue levels of ACE2. They reported that ACE2 levels are more in Asian females so they are infected less. Also, they explained that estrogen and testosterone modulate ACE2 expression levels. With this confliction this study was performed to evaluate the clinical features of 68 Novel Coronavirus 2019-infected cardiac cases in Ilam, IRAN and check whether the symptoms show any difference between men and women in these Coronavirus 2019-Infected cases with pre-existing cardiovascular diseases.

METHODOLOGY
A single-center, retrospective observational study was done at Mostafa Khomeini Hospital in Ilam Province, Iran, from January to March 2020. Data of 68 Cardiac patients who diagnosed covid 19 infections were reviewed, after the approval of ethical committee of Ilam university of medical sciences, Ilam, Iran (Ethics ID: IR.MEDILAM.REC.1399.049). Data collection forms were reviewed by two researchers separately. The initial physical examination, the first signs and symptoms, pulse oximetry oxygen saturation (O2 SAT) and laboratory results, chest radiography and CT findings of 68 cardiac patients were evaluated and analyzed retrospectively. Blood group was also recorded. Supportive oxygen therapies (through mask or tracheal intubation) were also described. Electrocardiograph (ECG) also analyzed. Under safety conditions Nasopharyngeal and oropharyngeal sample collecting from the cases were done by experts, then samples were transferred to the special lab for coronavirus laboratory in the insulated boxes equipped with cool pack (4 °C). The viral RNA was extracted from the sample, using the extraction of viral DNA/RNA kit (Favorgen Biotech Corporation, Taiwan) and kept at −20°C to the time of test operation. PCR amplification was done in accordance to Sansure Biotech Inc. kit producer instruction (Changsha, China). The specific primer and probe RT-PCR targeting ORF1ab and Nucleoprotein gene (N genes) were utilized to detect the viral genomes of the SARS-CoV-2 in patients’ samples. As well as, internal control targeting the RNase P gene used for monitoring process sample collection and PCR reaction in order to minimize false-negative results. For the cycle's threshold (CT) values more than 40 cycles, the test result was reported as negative. For real-time PCR reaction, first 30 μL Master Mix and then 20 μL of the extracted viral RNA were added into each well. PCR tubes were placed within the Mic Real-Time PCR System (Bio Molecular Systems, Australia). The rRT-PCR test was completely performed about 124 min and the fluorescent curves were observed to analyze the result. Positive results with a CT value less than 40 cycles confirmed the existence of SARS-CoV-2 RNA.

In each detection run, a negative control (no template) was used in order to check any contamination during the rRT-PCR procedure, as well, a positive template control used to observe whether the rRT-PCR process operated properly. Statistical analyses were done using SPSS software version 17.0. P values less than 0.05 were considered statistically significant. Continuous measurements were presented as mean if they were normally distributed, or median (IQR), if they were not, and categorical variables were presented as count (%). Laboratory results, also assessed whether the measurements were not in the normal values. Categorical variables have expressed as number (%) and compared by χ2 or Fisher’s exact and Mann Whitney tests between the groups.

RESULTS
This study consisted total 68 Cardiac patients with (rRT-PCR confirmed) SARS-CoV-2 infection referred to Ilam hospital. 52.9% of the patients were female (vs. 47.1% male) (Table 1). The mean ages were 70.84 ±1.8 and 68.72 ±1.7 years in males and female patients respectively, with no significant differences. The youngest was 43-year female, and the oldest was 91-year male. The most common symptoms at the beginning of illness were dry cough (78% of male versus 80% females) and fever (62% of male versus 75% females). The other signs and symptoms are presented in Table 1. Chest/Abdominal pain, hemoptysis, perspiration, and arthralgia were less common symptoms (Table1).

Patients’ temperature range was 36 to 40.3 °C. 75% of female and 62.5 % of male had fever (≥ 37.8°C) but there isn’t any significant difference between two genders. 97% of febrile patients needed oxygen supplementation (100% males versus 96% females) but there isn’t any significant relationship between O2 and fever. 81% of afebrile patients also received oxygen. Mean O2 saturation in patients who did not
received oxygen supplementation was ≥86%. O2 saturation in patients with O2 therapy was 85% (without any significant difference between men and women) (table1). There isn’t any difference between the ages of who required supplemental O2 compared with who did not require (69.7 vs. 69.6 years, p<0.98). 31% of men and 11% of women experienced intubation (significant difference between both genders).

Table 1: Clinical Symptoms of Patients with SARS-CoV-2 Infection

| Characteristics          | Male    | Female   | P value |
|--------------------------|---------|----------|---------|
| Total (N)                | 32 (74.1) | 36 (52.9) |         |
| Age, mean (range) years  | 70.84 (49-91) | 68.72 (43-90) | 0.38    |

Table 2: Laboratory Findings of Patients with SARS-CoV-2 Infection

| Blood routine, median (range) | Male | Female | P value |
|-------------------------------|------|--------|---------|
| Red blood cell (×10^12/µL)    | 4.40 (2.6) | 4.30 (3.5) | 0.19    |
| Leucocytes (×10^3/µL; normal range: 3.5–9) | 7.3 (3.8–21) | 7.3 (3.4–26) | 0.91    |
| Neutrophils (%; normal range: 40–70) | 80.50 (65–90) | 75 (60–91) | 0.1     |
| Lymphocytes (%; normal range: 20–50) | 19 (8–34) | 20 (9–40) | 0.08    |
| Platelets (×10^12/µL; normal range 150–450) | 191 (110–459) | 250 (121–518) | 0.035   |

Table 2: Laboratory Findings of Patients with SARS-CoV-2 Infection

| Blood biochemistry, median (range) | Male | Female | P value |
|------------------------------------|------|--------|---------|
| Serum creatinine (mg/dL; normal range 0.6–1.3) | 1.40 (1–11) | 1.30 (1–5) | 0.01 |
| Urea (mg/dL; normal range 8–65) | 53 (1–251) | 29 (1–152) | 0.01 |
| Na (mmol/L; normal range 136–148) | 136 (130–153) | 138 (132–152) | 0.33 |
| K (mmol/L; normal range 3.5–5.5) | 4 (3–6) | 3.9 (3–5) | 0.15 |
| Ca (mmol/L; normal range 2.2–2.7) | 2.2 (7.7–10.8) | 2.5 (8.3–10.9) | 0.13 |

At the chest CT, the features of pneumonia were found in 86–87% men and women cardiac patient with COVID-19 (Table 1). Most infected cardiac patient’s blood group was A+ (43.90% of total, 45.50% of males and 42.10% of females). There is not considerable difference between two genders from this view (Table 4). Males and females patients, respectively 53.10 and 52.8% shown sinus tachycardia (ST arrhythmia), with no significant differences among genders. Premature ventricular complex (PVC) was found in ECG of the 2.9% of total patients with no significant differences between genders. Bundle branch block (BBB) arrhythmia was found in ECG of the 31.20% of males vs. 11.10% of females with significant differences between genders (p<0.05). Only one
The mean systole and diastole blood pressures respectively were 130±4 and 79.7 ±2 in males and 134±4 and 81±3 in female patients, again with no significant differences between genders. The 43.80 and 27.8% of males and female patients respectively, shown heart axis changes, with no significant differences among genders (Table 4).

Table 4: Blood groups and Electrocardiographic findings of Patients with SARS-CoV-2 Infection

| Blood groups | Blood creatinine (mg/dl) | Serum creatinine (mg/dl) | Urea (mg/dl) | Troponin I (ng/l) |
|--------------|--------------------------|-------------------------|--------------|------------------|
| Male         | 4.18±0.30                | 1.48±0.30               | 14(56.0)     | 4(12.5)          |
| Female       | 4.18±0.30                | 1.48±0.30               | 6(18.8)      | 0                |
| P-value      |                          |                         |              |                  |

Of 68 patients 11% of females and 28% of males died, and the others discharged. Most of them were male. The mean age of expired patients was 72 with a range of (49-91) years. The medians of body temperature (37.34) and respiratory rate (18.23) of these patients were not significantly more than survived ones, and the O2 saturation detected by pulse oximeter was significantly less in these patients than survived ones (79.23%, p<0.01).

DISCUSSION

It has been pointed out that the association between hypertension and COVID 19 infections is likely due to their association with ACE II enzyme, additon to hypertension, other cardiovascular comorbidities were also frequently reported in patients with severe cases of COVID 19. Patients with pre-existing heart failure are more likely to have elevated ACE II expression which can increase the risk of infection. The present study revealed the prevalence of COVID-19 in male cardiac patients are little more dominant than females. Also, in the dead cases, men were more than women. Based on other studies, also male patients were more than female patients. There are many differences between both genders in the immune response to SARS-CoV infection and inflammatory diseases, and stated females, compared to males, are less susceptible to viral infection, because of difference in the innate immunity, their steroiodal hormones and some factors associated with sex chromosomes. A pair of X chromosomes in women supports the immune system and causes lower viral load, and less inflammation than in man. Most common clinical symptoms in male and female cardiac cases were cough, fever, dyspnea, and chills. Based on meta-analysis study generally fever in about 88 %, cough in 57%, and dyspnea in 45 % of patients were reported as the most prevalent clinical symptoms. In our study, Leukocytopenia was observed in 2.8% of females and 6.3% of males and leukocytosis in 30% of female and 37% of males. Neutrophilia was observed in 75% of both genders, lymphopenia in 38.9% of females and 58.4% of males, and thrombocytopenia was presented in 11.1% of men and 18.8% of women, without any significance between genders. Generally, a study expressed that almost 19 % of patients with covid-19 shown leukocytopenia, and 17%, leukocytosis, and 43% shown lymphopenia. SARS-CoV-2 induces lymphopenia probably via acting against lymphocytes, chiefly T cell. Spreading the virus via respiratory system, and infection the cells lead to increased cytokine releasing and induce sequences of immunity reactions causing change in lymphocytes. In a study 5% of patients showed less than 100×10⁹ platelet/L. But the other study reported a normal median range for platelet. Decrease in hemoglobin was detected in 75% of females and 56% of Males, like our study, decreased hemoglobin levels were shown by Chen and colleagues (51%), but the normal hemoglobin levels also reported in some study on SARS-CoV-2 infected patients. Percentage change of hemoglobin levels also may relate to the basic levels of hemoglobin and anemia in every area. Serum creatinine and urea increased above the normal levels.
respectively in 48 and 56% of males (versus 11 and 18% of females). BUN was increased in 6% and creatinine level, in 3% of covid-19 cases in a study. But normal median levels also were reported in severe cases of a study. A study in Iran reported that creatinine and urea respectively increased in 14 and 10% of their cases, in spite normal median range, also this study reported high levels of serum creatinine and urea in severe cases.

Troponin level was different between male and females, 12.5% of males shown increased levels of troponin. Arentz et al. shown that high troponin levels in 14% of their patient (> 300 ng/l); it indicates cardiac injuries; in a study 31% of ICU cases showed high troponin levels. Based on our study lymphopenia, neutrophilia, thrombocytopenia, high serum BUN and creatinine levels which declare that COVID-19 infection might be related to the cell immune deficiencies and renal injuries in these cardiac patients.

Most infected cardiac patients' blood group was A+. A study on 557 individuals with COVID-19 in Sudan reported that Rhesus-positive (A+) individuals were the most vulnerable. Of course, it should not be forgotten that A + is one of the most common blood types in the population.

Over 50% of males and female patients has shown ST arrhythmia, with no significant differences among genders. BBB arrhythmia was almost found in ECG of the 31.20% of males vs. 11.10% of females with significant differences between genders. The 43.80 and 27.8% of males and female patients respectively, shown heart axis changes. Based on studies occurrence of arrhythmias among COVID-19 cases who are clinically stable is low. In these cases, arrhythmias may result from hypoxia because of direct effects of SARS-CoV-2 on lung tissue, myocarditis, and also unusual immune reactions.

In accordance with this, over 90% of our patients needed oxygen therapy because of hypoxia and the Mean O2 saturation in our patients with O2 therapy or not was 85-86%; furthermore 31% of men and 11% of women experienced invasive mechanical ventilation. Also, it is stated that arrhythmias could result from other situations such as myocardial ischemia, myocardial strain, disturbing fluid and electrolytes balance, and medicines side effect. As well Arrhythmias may appear in presence of systemic diseases, not with direct effect of SARS-CoV-2 infection. It should be mentioned that heart axis changes might directly cause by our patients’ chronic cardiac disease and hypertension.

Our study shown pneumonia were found in 86-87% men and women cardiac patient with covid19. Also, the other studies reported bilateral pneumonia and ground-glass opacities on chest CT scans of patient with SARS-CoV-2 infection.

At last, in our study, 13 patients died (11% of females and 28% of males). This is different among studies. O2 saturation in deceased patients was significantly less than in survived ones (79.23%). A study has reported 19% of hospitalized patients died and surprisingly all of the expired cases were male with ages over 50 years. A meta-analysis study showed 13.9% non-survived cases among hospitalized ones.

**CONCLUSION**

Cardiac diseases and hypertension are probably among the most sensitive and high-risk groups for COVID-19 disease. Clinical symptoms reported among COVID-19 patients with pre-existing cardiovascular disease have a wide range. Based on this study the severity of symptoms and outcomes of COVID-19 in cardiac patients showed some differences between men and women which could be related to differences in immune responses, respiratory tract properties, renin angiotensin system, sex hormones and lifestyle. However, more studies and follow-up of patients in terms of final results and identification gender differences in this group of patients are required.

**AUTHORS' CONTRIBUTION**

EM: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. MRK, IA, AK, AS, SN, FB, AG, EB, MR, MK, MF, SF, GK, MM: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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