Cardiovascular System during SARS-CoV-2 Infection

Subjects: Cardiac & Cardiovascular Systems

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SARS-CoV-2 virus can not only damage the respiratory system but may also pose a threat to other organs, such as the heart or vessels. It was focused on cardiovascular complications of COVID-19, including acute cardiac injury, arrhythmias, biomarkers, accompanying comorbidities and outcomes in patients diagnosed with SARS-CoV-2 infection. The results show that cardiac injury is present in about 1 in 4 patients with COVID-19 disease, and it is an independent risk factor, which multiplies the death rate several times in comparison to infected patients without myocardial injury.

coronavirus disease 2019 cardiac injury cardiac complications

1. Cardiac Injury

1.1. Frequency and Characteristic

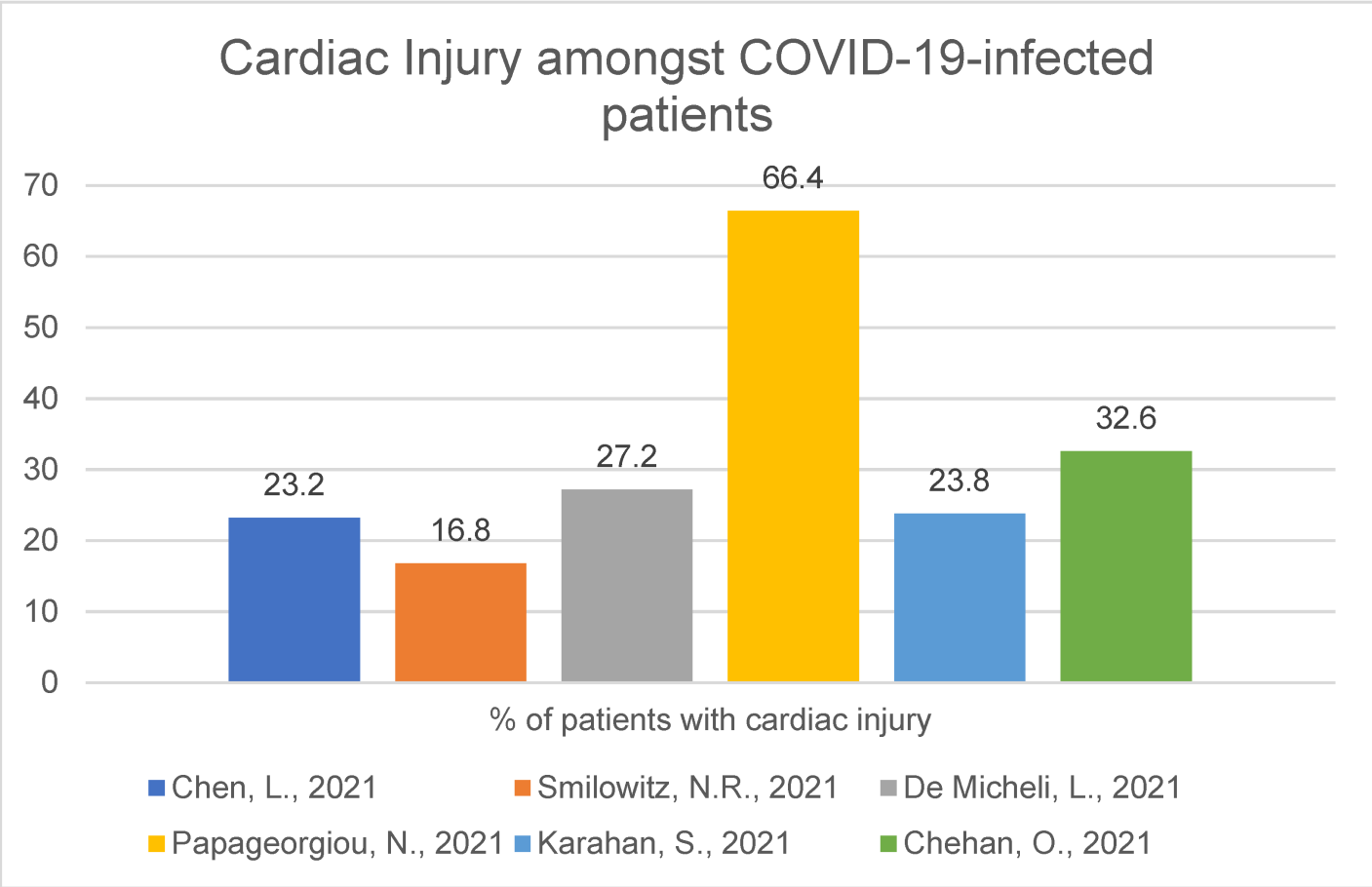

Figure 1. Cardiac injury amongst COVID-19-infected patients [1][2][3][4][5][6].

Critical or severe patients have higher levels of troponin during hospitalisation and are more likely to have a cardiac injury with the range from 28.3% to 51% [7][8][9][10]. For 330 patients, cardiac injury (based on hs-cTnI levels) was diagnosed in 32.4% of patients (104), and the whole group consisted of only severe and critically ill COVID-19-positive patients [8]. In the multi-centre one of 2878 SARS-CoV-2-positive critical patients in France, troponin was elevated above each centre's threshold in 32.4% and in 58.5% of the deceased group [10]. For 243 intubated COVID-19-positive patients from five different hospitals, 51% had troponin levels above the upper limit [9]. Another for 201 SARS-CoV-2-positive patients with myocardial injury (based on cTnI) shows that troponin was elevated above the normal level of 0.04 ng/mL in mild patients and three times over the threshold (>0.12 ng/mL) in critical patients (28.3%, $p < 0.001$, critical patients were those who needed mechanical ventilation) [7]. In another article of 218 patients with myocardial injury, there were also major differences in troponin elevation between critical and mild COVID-19-positive patients (28.8% critical vs. 4.8% non-critical, $p < 0.0001$) [11].

The situation is different when speaking of first-detected cardiac injury. Here the numbers are lower with a range: 2.9–10.8%. A Chinese one has revealed that hs-cTnI (high-sensitivity cardiac troponin type I) was elevated in COVID-19-positive patients in 10.8% of 218 enrolled patients (mean age was 62 (IQR: 55, 69) years). These patients presented without previous cardiovascular symptoms or past medical history involving cardiovascular disease and were admitted to the hospital because of typical SARS-CoV-2 symptoms [11]. In the American one, 179

patients (mean age 59.8 ± 16.9 years), myocardial injury was present in only 7% of patients (significant troponin level elevation accompanied by new ventricular dysfunction or electrocardiographic abnormalities) [12]. Scientists from the King's College of London conducted a randomised one of 172 SARS-CoV-2-positive patients (mean age 55.1 ± 13.9 years), which showed that 10.2% developed a major cardiac injury (peak hs-cTnT >20× ULN) [13]. In the previously presented analysis, new cardiac abnormalities occurred in 3.9% of 434 COVID-19-positive patients [4]. Concerning athletes, a study showed that only 2.9% had abnormal newly-detected cTnI levels with no serious symptoms (laboratory 99th percentile, 0.035 ng/mL.). All these athletes were referred for CMR. No athlete had abnormal findings detected by CMR: no ventricular dysfunction, delayed myocardial enhancement, abnormal T2 weighted imaging or pericardial pathology. Limitations is that it did not use hs-cTnI [14]. The four previously mentioned ones [4][11][12][13] are assembled in the figure below (**Figure 2**). The information from [14] is not included in the figure because it concerns athletes.

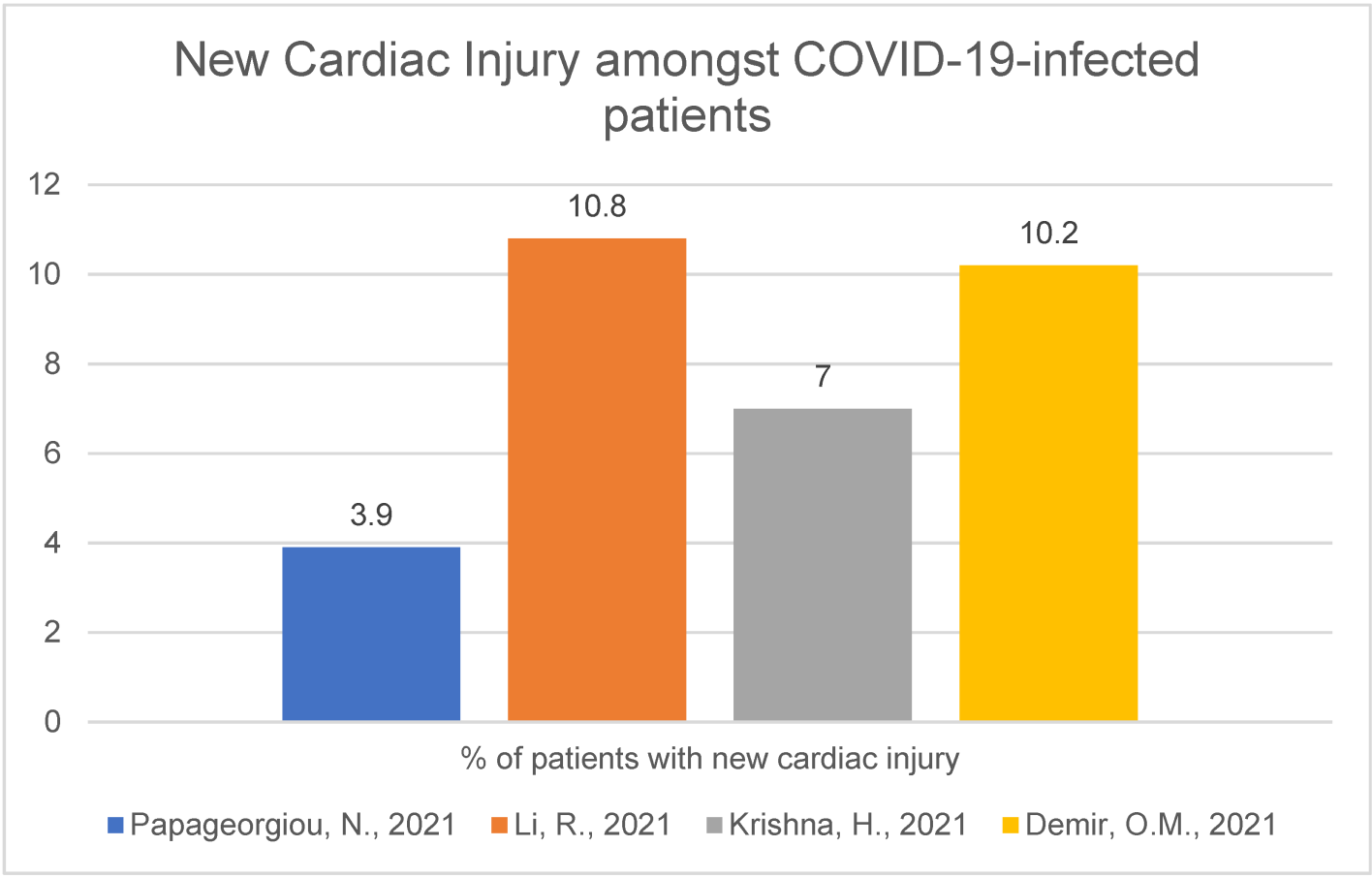

Figure 2. New cardiac injury amongst COVID-19-infected patients [4][11][12][13].

Critical or severe patients have higher levels of troponin during hospitalisation. In Wuhan, 40 (30.3%) consecutive patients displayed acute cardiac injury (based on hs-TnI above the 99th-percentile upper reference limit, mean age 61 ± 13 years) [15]. These could be due to more critical cases (62.1% severe or critical).

1.2. Hospitalisation and Outcome

23 articles was used in this section. Cardiac injury was a crucial and independent risk factor for mortality in COVID-19-infected patients [6][15][16][17] and mortality was usually higher in the cardiac injury group [1][3][17][18][19]. Patients with cardiac injury were older [1][5][16][20], had more comorbidities [16][19][20], were mostly male [4][16], had more serious disease [1][16][17] or were more likely to require mechanical ventilation [15][16]. Age is an independent predictor of myocardial injury in COVID-19-positive patients [4]. Critical patients with myocardial injury (serum troponin I > 99th percentile ULN) are more likely to die [5] (17 times more likely) or develop ARDS [5] (11.5 times more likely) than those without myocardial injury. Critical patients with higher troponin levels (>10 ULN) were more likely [9] (2.7 times more likely) to die than those with any troponin elevation (< ULN). Critical patients with high hs-cTnI (>28 pg/mL) levels were more likely to die [21] (2.637 times more likely, 95% CI, 1.058-6.570, $p = 0.037$)) than those with low levels, as well, hs-cTnI was an independent risk factor of mortality [21] in these patients, which indicates that hs-cTnI levels may be useful in assessing mortality risk in critically ill patients with COVID-19. Elevation of cardiac biomarkers is an independent predictor of mortality [1][2][10][12][13][22][23][24][25] or severity of illness [4], even in patients with no previous history of CAD or heart insufficiency [10]. These are myoglobin [1], CK-MB [1] and troponin [2][4][12][13][22][23][24][25][26]. Length of stay at the hospital in days is shorter for patients with negative troponin levels [4]. For 196 COVID-19-positive patients that showed that cTnI (≥21 ng/L) is a better prognostic value for 30-day all-cause mortality in comparison with CRP, LDH and D-Dimer [25]. A previously presented one of 181 COVID-19-positive patients showed patients with cardiac injury were older and had more comorbidities (most common were hypertension, coronary heart disease and arrhythmias), and the cardiac injury group (42 patients) required noninvasive ventilation more often (20 (47.6%) vs. 14 (10.1%), $p < 0.001$), more often had severe disease (36 (85.7%) vs. 47 (33.8%), $p < 0.001$) and mortality was much higher in the cardiac injury group (22 (52.4%) vs. 12 (8.6%), $p < 0.001$) [1]. The situation is no different in another one where the COVID-19-positive group was associated with a more severe presentation of SARS-CoV-2-infection (critically severe, 26.0% vs. 7.2%, all $p < 0.001$). Compared with those without myocardial injury, more COVID-19-positive patients with myocardial injury required oxygen inhalation, non-invasive ventilation, invasive mechanical ventilation, antibiotic treatment and hemoperfusion therapy (all $p < 0.001$). Mortality rate was significantly higher in patients with myocardial injury (63.5% vs. 13.0%, $p < 0.001$) [16]. For 400 COVID-19-positive patients show that those with cardiac injury (troponin >99th percentile) were older (52.5 (42.8–68.0) vs. 49.0 (36.0–0.0) years), myocardial injury event was much higher in patients with comorbidities: hypertension (12/46 (26.1%) vs. 50/354 (14.1%)), hyperlipidemia (4/46 (8.7%) vs. 7/354 (2.0%)) and chronic kidney insufficiency (3/46 (6.5%) vs. 2/354 (0.6%)) [20]. For 226 patients, the rate of myocardial injury and myocardial infarction were significantly higher among deceased patients as compared with those who recovered (54.4% vs. 20.3%, $p < 0.001$; 20.6% vs. 6.3%, $p = 0.003$) [18]. For 367 patients showed that patients with myocardial injury have more comorbidities than patients without myocardial injury (hypertension: 78% vs. 42%, diabetes 44% vs. 21%, coronary artery disease 17% vs. 5.1%). Patients with myocardial injury had a higher risk for short-term mortality than those without myocardial injury (20% vs. 12%, $p < 0.0001$; unadjusted HR 4.44, 95% CI 2.13–9.25, $p < 0.001$) and for major adverse events (35% vs. 11%, $p < 0.0001$; unadjusted OR 4.29, 95% 2.50–7.40, $p < 0.0001$) [19]. In another research of 324 COVID-19-positive patients, death occurred in 54.5% and 3.2% of the patients with and without myocardial injury, respectively. Notably, 75.3% of patients with myocardial injury and 6.5% without myocardial injury developed ARDS. The median serum troponin I levels were 306 (72–852) and 2.5 ng/mL (1.3–5.5) in the deceased and surviving patients,

respectively ($p < 0.001$) [5]. In the group of 243 critical patients, mortality was listed at the level of 22.7% among patients with COVID-19 and troponin over the upper limit of normal value (0.04 ng/mL) and 61.5% for those COVID-19-positive and troponin levels >10 times the upper limit of normal value ($p < 0.001$) [9]. Hs-cTnI was an independent marker for a critical outcome in a group of 726 COVID-19-positive patients (>28 pg/mL) (OR, 2.899; 95% CI, 1.743–4.822, $p < 0.0001$) [2]. For 2873 SARS-CoV2-infected patients, indicated that nine variables were independent predictors for in-hospital mortality, including troponin (HR: 2.150; 95% CI: 1.155–4.001; $p = 0.016$) [22]. Next, research of 880 COVID-19-positive patients pointed out that initial hs-cTnT (high-sensitivity cardiac troponin type T) was associated with composite adverse outcomes with a median hs-cTnT of 11 ng/L in patients who were living and did not require mechanical ventilation versus 31 ng/L in patients who expired or required mechanical ventilation [27].

An interesting one showed that there is no association between the initial viral load (iVL) and cardiac injury (based on increased >100 ng/L hs-cTnI level); however, both iVL and cardiac injury were independent predictors of mortality [6].

1.3. Myocardial Infarction

Myocardial infarction in COVID-19-positive patients is not common [3][19][28]. For 346 patients with elevated hs-cTnT conducted in the UK has demonstrated that there were no COVID-19-positive patients in the group of 115 patients with Type 1 MI, and in the group of 231 patients with Type 2 MI/myocardial Injury there were 36 (16%) patients who were COVID-19-positive. Cardiac causes of MI were more common in patients without SARS-CoV-2 virus (positive: 11.1% vs. negative: 33.3%, $p = 0.22$), of which tachyarrhythmia and heart failure were the most likely mechanisms (15.7% and 15.1%) [28]. Next, for 313 patients of whom elevation was present in 85 patients (27.2%) and of those 85 patients, only 11.7% had criteria for MI: 7% had type 2 MI, and 4.7% had type 1 MI [3]. In another of 367 patients, only 5% of patients with elevated troponin (169) were adjudicated as acute MI, with three patients classified as type 1 MI and five patients as type 2 MI [19].

1.4. Myocarditis

Acute myocarditis occurred in some COVID-19 patients and was usually focal but not common [19][29]. With the biggest number of patients (1160) showed that acute myocarditis in COVID-19 patients developed in only 1% of cases [29]. Pericardial effusion was seen more frequently [15] (9%), [30] (9%). Another work of 367 patients showed that myocarditis was rare with clinical suspicion in only three patients in whom there was no definite confirmatory testing with cardiac magnetic resonance imaging or biopsy [19].

In the population of athletes, myocarditis or pericarditis was not common. Only 0.4% of athletes had myocarditis after COVID-19 infection [31], and 0.26% had pericarditis [31].For another, 3% had myocarditis [32], and 1.5% had pericarditis [32], usually without symptoms.

The situation is different in severe and critical COVID-19 patients. In UK, concerning 148 severe COVID-19-positive and troponin(+) patients who underwent CMR (cardiac magnetic resonance), pericardial effusion was seen

in 8/148 (5%). A total of 47/148 patients had a non-ischaemic pattern of myocardial injury, and 40/148 patients had a myocarditis-pattern injury (including four with coexisting inducible ischaemia and three with coexisting myocardial infarction). In the group of patients with myocarditis-pattern injury, only 12 (8% from the whole population) had findings consistent with active myocarditis (8 with a regional elevation of both native T1 and T2, 4 with a regional elevation of T2 only) [30].

2. Arrhythmias

2.1. Hospitalisation and Outcome

Eight articles were used in this section. Patients with new-onset arrhythmias were older [33][39][40] and presented more frequently with some comorbidities (hypertension, diabetes, cardiovascular artery disease or valvular heart disease) at admission [33][39][40] and stayed longer in hospital in comparison with the non-arrhythmia group [40]. Patients with arrhythmias were in general more likely to have some comorbidities [41]: hypertension (153 (38.6%) vs. 17 (25.4%); $p = 0.04$), coronary heart disease (21 (24.7%) vs. 29 (7.7%); $p < 0.001$) and diabetes mellitus (20 (23.5%) vs. 52 (13.8%); $p = 0.025$). It was mentioned before of 517 patients, those with new arrhythmias were older (81.6 vs. 66.5 years old, $p < 0.001$) and more frequently presented hypertension (74% vs. 47%, $p < 0.001$), cardiomyopathy (9% vs. 1%, $p = 0.002$), previous heart failure admission (9% vs. 0.4%, $p < 0.001$), previous episodes of atrial fibrillation (83% vs. 1%, $p < 0.001$) and bigger left atrium (47.8 vs. 39.9 mm, $p < 0.001$) [39]. However, there was one of 1029 COVID-19-positive patients that demonstrated that patients with new-onset arrhythmias were significantly younger compared to patients with previous arrhythmia or without, and also had higher BMIs ($p < 0.05$). Patients with new-onset atrial arrhythmia less often had a history of heart failure and coronary artery disease compared with recurrent and chronic persistent atrial arrhythmias patients ($p < 0.05$) [42]. More critical COVID-19-positive patients developed more arrhythmias compared to patients with mild or without symptoms [7][33][43][44], whilst in one of these, 28.6% of patients (critical) and 17.9% of patients (severe) presented with arrhythmia in the new arrhythmia group compared with 7.2% (critical) and 8.8% (severe) in the non-arrhythmia group ($p <0.001$) [33]. For 463 COVID-19-positive patients, the proportion of critically ill patients was higher among patients with arrhythmias than those without arrhythmias (38 (44.7%) vs. 80 (21.2%); $p < 0.001$), suggesting an association between arrhythmias and adverse COVID-19 outcomes, and the all-cause mortality rate was higher in patients with arrhythmias than in those without arrhythmias (22 (25.9%) vs. 38 (10.1%); $p < 0.001$). Survival analyses showed that arrhythmias were associated with a high mortality rate ($p < 0.001$) [41]. In Bologna, Italy, 106/216 COVID-19-positive patients had abnormal ECG at the beginning of hospitalisation and increased troponin values occurred more often in patients who developed major adverse events ($p = 0.04$ and $p = 0.02$). Concerning ECGs after 7 days (159), abnormal findings were reported in 53.5% of patients, and they were more frequent in those with major adverse events (MAE, $p = 0.001$). The multivariable analysis showed the presence of abnormal ECG at 7 days of hospitalisation was an independent prediction factor of a major adverse event (HR 3.2; 95% CI 1.2–8.7; $p = 0.02$) [43].

2.2. Accompanying Comorbidities

Twenty-nine articles were used in this section. COVID-19-positive patients with more comorbidities are associated with a more severe duration of illness [7], more often require intensive care [45] or are at a higher risk of death [5][10][18][46]. Male sex is prevalent among patients who died during hospitalisation [17][18][21][47][48] and is associated with higher mortality [17][46]. Age is an independent predictor of higher mortality in COVID-19-positive patients [10][45][46][49][50], increasing the risk of intensive care necessity [45] or illness severity [21]. Cardiovascular artery disease [45][46], diabetes mellitus and hypertension [45] are associated with higher mortality amongst COVID-19-positive patients and associated with intensive care or mechanical ventilation [45]. Critical patients are more likely to have the underlying cardiac disease [17], more comorbidities [7], to be male [7][17] and older [7][17][44]. About one-quarter of patients with heart failure die when they get infected with the SARS-CoV-2 virus [47]. There was a large one of 1,212,153 patients with a history of HF (heart failure), 8383 of which were COVID-19-positive (The Premier Healthcare Database), which concluded that patients with HF hospitalised with COVID-19 are at high risk for complications, with 24.2% dying during hospitalisation. Those who suffered from COVID-19 and had a past history of HF were more likely to have post-hospitalisation care (41% vs. 13%) or were referred to hospice (6.7% vs. 4.1%) than COVID-19-negative patients with HF. Patients with a previous history of HF and COVID-19 had significantly greater in-hospital resource use (mechanical ventilation, central venous catheter insertion) compared with patients hospitalised with acute HF and without COVID-19 (Intensive Care Unit care 29% vs. 15%, mechanical ventilation 17% vs. 6%, venous catheter 19% vs. 7%) Mortality amongst COVID-19 patients was greater in patients with acute heart failure 24.2% vs. 2.6% [47].

For 324 COVID-19-positive patients shows us that hypertension and chronic kidney disease were significantly more common among the deceased compared with surviving patients. Myocardial injury was present in 84% of the deceased group, whereas 12.8% of the surviving patients had a myocardial injury ($p < 0.001$) [5]. One interesting one for 320 COVID-19-positive patients showed that predictors for elevated troponin levels were age (odds ratio (OR), 1.04; 95% confidence interval (CI), 1.01-1.06), female sex (OR, 3.03; 95% CI 1.54–6.25), low systolic blood pressure (OR, 5.91; 95% CI 2.42–14.44) and increased creatinine level (OR, 2.88; 95% CI 1.44–5.73) [26]. For 2878 COVID-19-positive hospitalised patients conducted in France showed 72.6% had at least one, 41.6% had at least two and 19.9% had at least three cardiovascular risk factors, as well, it showed that male sex (HR 1.69, 95% CI 1.11–2.57; $p = 0.01$), older age (hazard ratio (HR) 1.05, 95% confidence interval (CI) 1.03–1.06; $p < 0.001$), diabetes (HR 1.72, 95% CI 1.12–2.63; $p = 0.01$), chronic kidney failure (HR 1.57, 95% CI 1.02–2.41; $p = 0.04$) and elevated troponin (HR 1.66, 95% CI 1.11–2.49; $p = 0.01$) were independently associated with in-hospital death [10]. In the next, 29% of 1169 COVID-19-positive patients in Italy had a previous history of some cardiac disease. Of these 29%, 60% had hypertension, 40% heart failure, 35% coronary artery disease and 25% atrial fibrillation. Only 18% had no comorbidities [29]. In a group of 1034 COVID-19-positive patients, these with some cardiovascular problems (who according to American Society of Echocardiography needed trans-thoracic echocardiogram) were more often admitted to ICU than those without any implications for examination (58.3% vs 18.9%) [51]. For 355 individuals demonstrated that patients with cardiovascular artery disease are at significantly higher risk of inpatient death than patients without cardiovascular artery disease (31% vs. 20%, $p = 0.046$), also age is significantly associated with higher mortality (1.041, 95% CI: 1.017–1.066, $p = 0.001$) in COVID-19 infected patients [46]. Another was previously presented that 226 patients demonstrated male sex was significantly dominant in patients

who died during hospital stay compared to those who recovered (75% vs. 57%, $p = 0.016$), and thirty-six patients underwent percutaneous coronary intervention, which was significantly prevalent in the deceased cohort (11.8% vs. 3.2%, $p = 0.025$) [18]. In Korea, 2269 COVID-19-positive patients demonstrated that diabetes mellitus ($p < 0.001$) and hypertension ($p < 0.001$) were associated with the increased requirement of intensive care and invasive MV (mechanical ventilation) and in-hospital death. Coronary artery disease (22.2% vs. 2.7%; $p < 0.001$) was associated with invasive MV. Coronary artery disease (33.3% vs. 7.1%; $p = 0.002$) and congestive heart failure (31.8% vs. 6.3%; $p < 0.001$) were associated with in-hospital death. Diabetes mellitus (OR, 2.43; 95% CI, 1.51–3.90; $p < 0.001$) and congestive heart failure (OR, 2.43; 95% CI, 1.06–5.87; $p = 0.049$) were independent predictors of in-hospital death [45]. Here was presented the percentage of infected patients with the most common comorbidities: Hypertension (**Figure 3**), diabetes (**Figure 4**), cardiovascular disease (**Figure 5**).

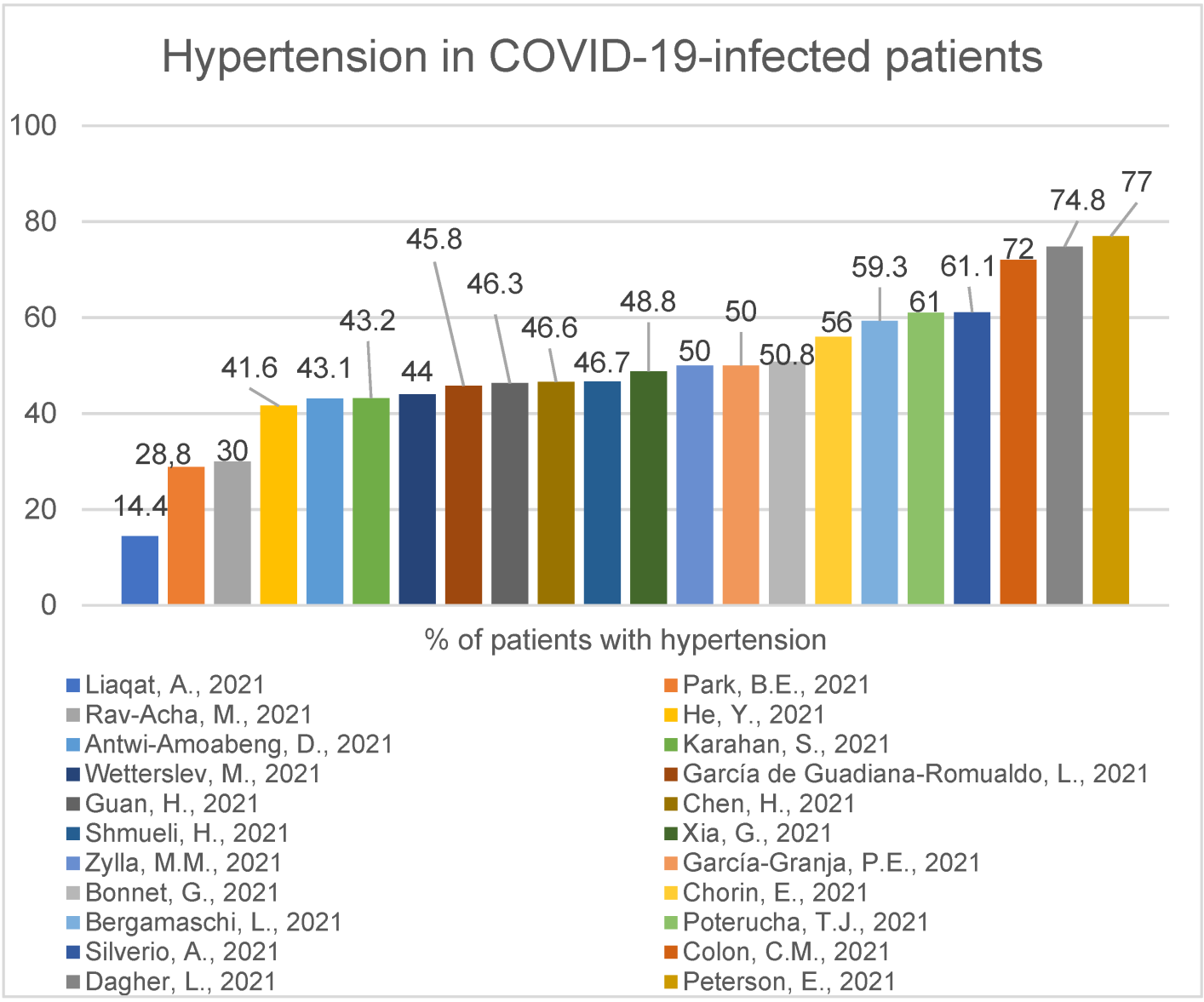

Figure 3. Hypertension in COVID-19-infected patients (median—47.8) [5][7][8][10][18][21][22][24][27][33][35][36][37][39][41][43][45][46][50][51][52][53].

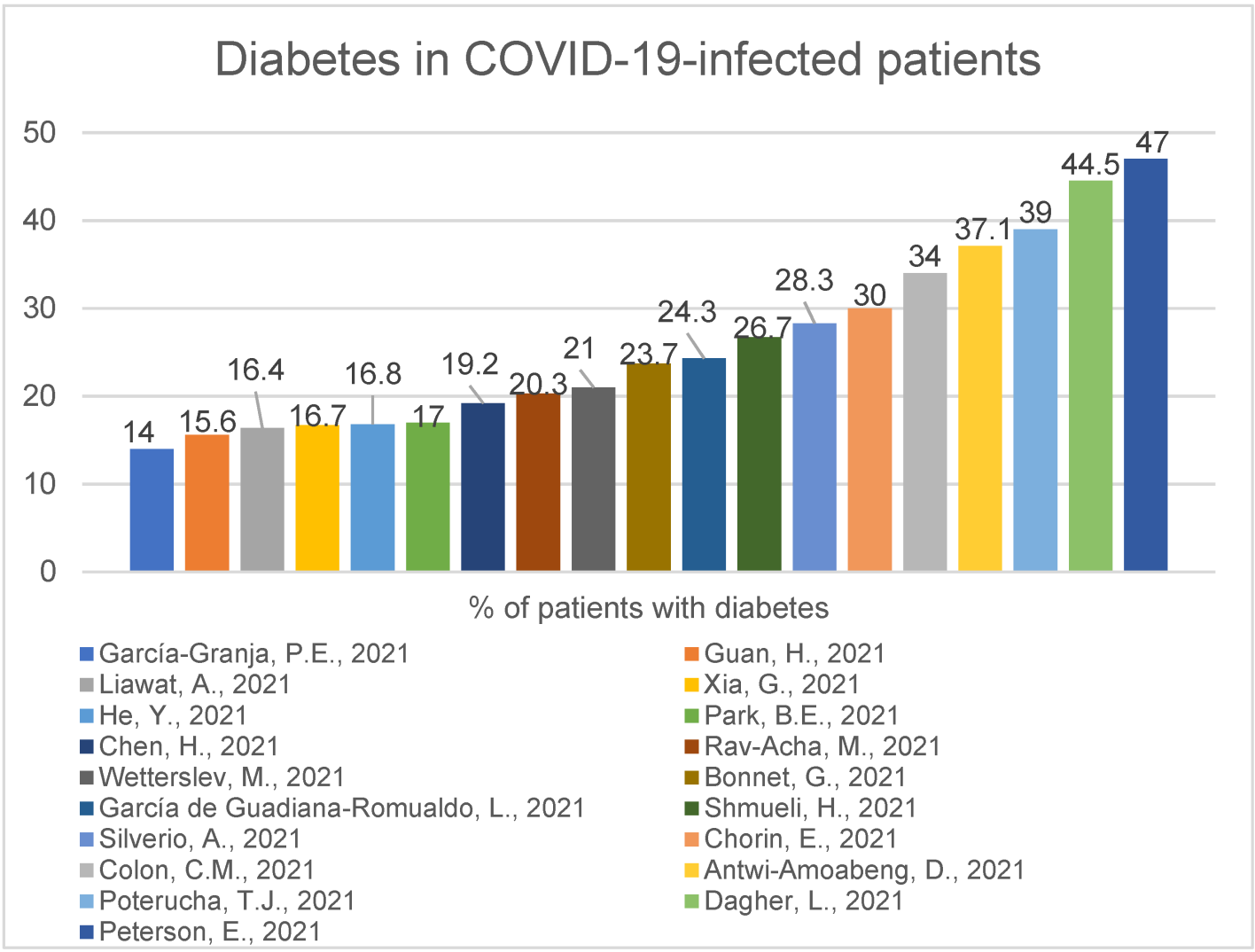

Figure 4. Diabetes in COVID-19-infected patients (23.7—median) [7][8][10][18][21][22][24][27][33][36][37][39][41][45][46][50][51][52][53].

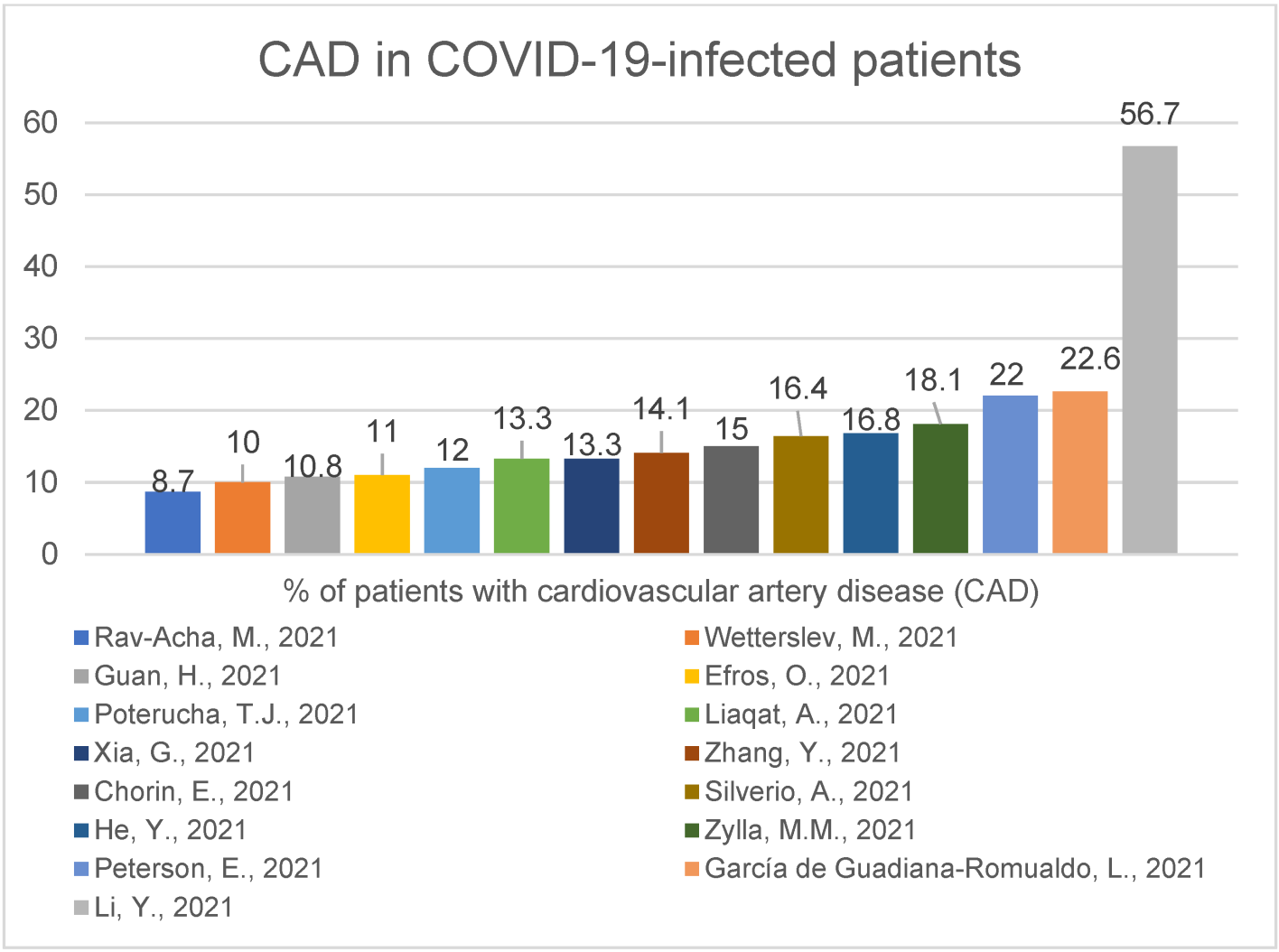

Figure 5. CAD in COVID-19-infected patients (14.1—median) [7][8][17][18][22][24][26][27][33][35][41][46][48][50][52].

There are some values that are clearly different from the majority. This may be caused by population heterogeneity, such as higher percentage of male population presented in the study [18][27][43][53], higher age [18][43][46], higher percentage of black race [37][46] or ICU sample [53]. In [46], it was selected patients with and without CAD to compare these two groups. For the highest numbers, four were performed in the USA [27][37][46][53] and two in Italy [18][43]. In an article from Pakistan [8], the mean age of patients is lower than in the vast majority of other articles (44.6 ± 15.2).

There are some values that are clearly outstanding and, similar as in **Figure 3**, this may be caused by population heterogeneity, such as higher percentage of the male population presented in [27][53], higher age [46], the higher percentage of black race [37][46] or ICU sample [53]. In paper [46], the authors selected patients with and without CAD to compare these two groups. All five with the highest numbers were performed in the USA [27][36][37][46][53].

In paper [48], the percentage of patients with CAD is outstanding due to learn design and chosen population sample: it was compared SARS-CoV-2-infected patients with CAD to SARS-CoV-2-infected patients without CAD.

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