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Analysis of the Influence of Comorbid States on COVID-19 Severity and In-Hospital Mortality for Further Application in an Outpatient Setting

Introduction. The COVID-19 pandemic brought many challenges to the healthcare systems of all countries. The spread of the infection led to an influx of patients that needed treatment, while specific guidelines were still being developed and medical logistics were spread thin [33]. Primary care physicians were on the front-lines, handling outpatient care, performing triage, consulting patients on potential risks, symptoms of concern and treatments options. On the other hand – in patient hospitals were packed with COVID-19 patients of differing severity. And although emergency and intensive care units have been using severity scales like the National Early Warning Score (NEWS), NEWS2, quick COVID-19 severity index (qCSI), Brescia-COVID Respiratory Severity Scale (BCRSS) to quickly asses patient severity and adjust care accordingly, these metrics only apply for an inpatient setting and don't provide much use for outpatient care and management [25, 34, 88]. Such a score system for family physicians and primary care providers can facilitate triage and help isolate high priority patients that need more in-depth care and diagnosis. By isolating main risk factors for developing severe COVID-19, a tool like this can be created for quick evaluation in an outpatient setting.

The aim of the study. To analyze available research data regarding the most common comorbid states of patients with a confirmed COVID-19 infection during in-hospital treatment and the role they play in disease severity and mortality. And based on the research data - to evaluate the possibility of developing a score system for outpatient use.

Materials and methods. Articles on COVID-19 patient care, disease progression, comorbidities and outcomes were gathered from the PubMed using a combination of keywords: COVID-19 (main search keyword), obesity, cardiovascular disease (CVD), hypertension, diabetes, liver disease (LD), asthma, chronic obstructive pulmonary disease (COPD), severity, outcomes. Articles were excluded based on the following criterial: patient groups consisting of children under the age of 18 and pregnant women, the lack of calculated odds ratios (OR) and patient groups with high risk underlying conditions without multivariable analysis to exclude interference in the results.

The data is analyzed based on two main outcomes for each comorbidity – severe disease (including in patient ICU transfer) and in hospital mortality.

Statistical analysis was performed using Jamovi 2.3 [83].

Results and discussion. In total 77 articles were chosen based on the defined criteria: 28 articles provided ORs for obesity, 32 - cardiovascular diseases, 42 - diabetes, predominantly type II, 10 - liver disfunction and/or disease, 11 - asthma, 21 - age of 61 and higher, 27 - chronic respiratory disease (including COPD), 31 - arterial hypertension (table 1).

Table 1

List of articles and the comorbid states that were evaluated in the article

Article	Obesity	CVD	Diabetes	LD	Asthma	Age 61+	COPD	Hypertension
1	2	3	4	5	6	7	8	9
Martos-Benítez FD (2021) [49]	*	*	*		*	*	*	*
COVID-ICU Group (2021) [17]	*		*			*		*
Al-Sabah S (2020) [5]	*		*			*		*

Contin of the tabl. 1

1	2	3	4	5	6	7	8	9
Cao P (2021) [13]	*		*			*		
Kadowaki T (2023) [42]	*							
Dana R, Bannay A (2021) [20]		*	*				*	*
McNeill JN (2021) [53]	*							
Sandoval M (2021) [65]	*	*	*		*			
Silva NJ (2021) [73]	*							
Schönfeld D (2021) [69]	*	*	*	*	*	*	*	*
Sjögren L (2021) [74]	*							
Gao M (2021) [29]	*		*					
Suresh S (2021) [78]	*							
Hajifathalian K (2020) [35]	*							
Cavallaro M (2021) [14]	*	*	*	*	*		*	*
Rossi AP (2021) [63]	*							
Alharbi AM (2022) [4]		*	*			*	*	*
Oblitas CM (2022) [58]			*			*		
He Y (2022) [36]			*					*
Kunal S (2020) [45]								*
Bonnet G (2021) [9]		*	*			*		*
Yan Y (2020) [91]			*					
Muñoz D (2023) [56]		*			*	*	*	*
Souissi S (2024) [75]						*		
Bauer AZ (2021) [7]		*	*	*			*	*
Bhatia KS (2021) [8]		*	*				*	*
Huang S (2020) [38]								*
Dai LS (2022) [19]								*
Shalaeva EV (2022) [70]	*	*	*					
Javanmard S (2021) [41]		*	*				*	
Nasir N (2021) [57]						*		
de Souza R (2021) [22]								*
Stanetić K (2021) [76]								*
Quenzer FC (2023) [60]	*							
Yacobitti A (2021) [89]		*	*			*	*	*
Maximiano Sousa F (2021) [51]								*
Terada M (2021) [81]	*	*	*	*	*		*	*
Rai DK (2022) [62]						*		
Santos VBD (2022) [66]	*							
Kubiliute I (2023) [44]	*	*					*	
Bravi F (2020) [10]		*	*			*	*	*
Islam MZ (2020) [39]						*		
Escalera-Antezana JP (2020) [26]						*		*
Vergara P (2023) [86]			*					
Jackson BR (2021) [40]						*		
Cordova E (2021) [16]	*	*	*			*	*	*

End of the tabl. 1

1	2	3	4	5	6	7	8	9
Aguiar-Brito I (2022) [3]								*
Motta JC (2020) [55]			*		*			
de Souza CD (2020) [21]			*			*		*
Cummings MJ (2020) [18]		*	*				*	*
Svensson P (2021) [80]	*	*	*		*		*	*
Lucar J (2021) [48]			*					
Girardin JL (2021) [30]	*		*		*		*	*
Caliskan T (2020) [12]		*					*	
Tessitore E (2021) [82]	*	*	*				*	
Fox DK (2022) [27]		*						
Toppen W (2022) [84]							*	
Agarwal MA (2020) [2]		*						
Vera-Zertuche JM (2021) [85]	*							
Santus P (2020) [67]						*		
Diedisheim M (2021) [23]			*					
Grasselli G (2020) [31]			*				*	
Sutter W (2021) [79]			*					
Sun Y (2021) [77]		*	*	*			*	*
Yakushiji Y (2022) [90]			*					
Gupta K (2022) [32]							*	
Kar S (2021) [43]		*	*	*		*		
Abifadel M (2024) [1]		*	*	*			*	
Bubenek-Turconi ŞI (2023) [11]		*	*					
Shukla AP (2021) [72]	*	*						
Barron E (2020) [6]			*					
McGurnaghan SJ (2021) [52]		*		*	*			
Galiero R (2020) [28]		*	*	*			*	*
Meister T (2022) [54]	*	*	*	*			*	*
Lee SC (2020) [46]					*			
Mash RJ (2021) [50]	*	*	*					
Sheikh D (2022) [71]							*	

Data about OR for patients with relevant risk factors compared to patients without ones, for severe disease course (including in-hospital ICU admission) and mortality were analyzed for each criterion. For obesity the OR for severe disease spanned from 1.1 (95% CI, 1.09-1.11) to 3.51 (95% CI, 1.60-7.69), for CVD - 1.02 (95% CI, 0.72-1.43) to 6 (95 % CI, 1.5-25.1), for diabetes - 0.91 (95% CI, 0.53-1.59) to 9.38 (95% CI, 5.49-16.02), for LD - 1.146 (95% CI, 0.83-1.58) to 2.18 (95% CI, 0.26-18.43), for asthma - 0.66 (95% CI, 0.15-2.82) to 2.3 (95% CI, 1.3-4.0), for patients older than 61 - 0.90 (95% CI, 0.54-1.53) to 6.93 (95% CI, 4.31-10), for COPD - 0.32 (95% CI, 0.08-1.21) to 5.80 (95% CI, 3.90-8.78), for hypertension - 0.73 (95% CI, 0.42-1.26) to 5.04 (95% CI, 3.32-5.26) (fig. 1, 3, 5, 7, 9, 11, 13, 15).

The OR for in-hospital mortality were as follows: obesity - 0.84 (95% CI, 0.58-1.2) to 7.18 (95% CI, 4.18-12.44), CVD - 0.92 (95% CI, 0.26-3.28) to 5.917 (95% CI, 1.069-32.258), diabetes - 0.56 (95% CI, 0.18-1.72) to 5.96 (95% CI, 5.64-6.3), LD - 0.33 (95% CI, 0.04, 2.45) to 5.67 (95% CI, 2.80-11.47), asthma - 0.83 (95% CI, 0.67-1.04) to 3.21 (95% CI, 1.00-10.30), patients older than 60 - 1.05 (95% CI, 1.03-1.06) to 13.5 (95% CI, 1.7-104.9), COPD - 0.83 (95% CI, 0.36-2.16) to 13.01 -95% CI, 3.24-52.28), hypertension - 0.73 (95% CI, 0.33-1.61) to 4.540 (95% CI, 1.203-17.129) (fig. 2, 4, 6, 8, 10, 12, 14, 16).

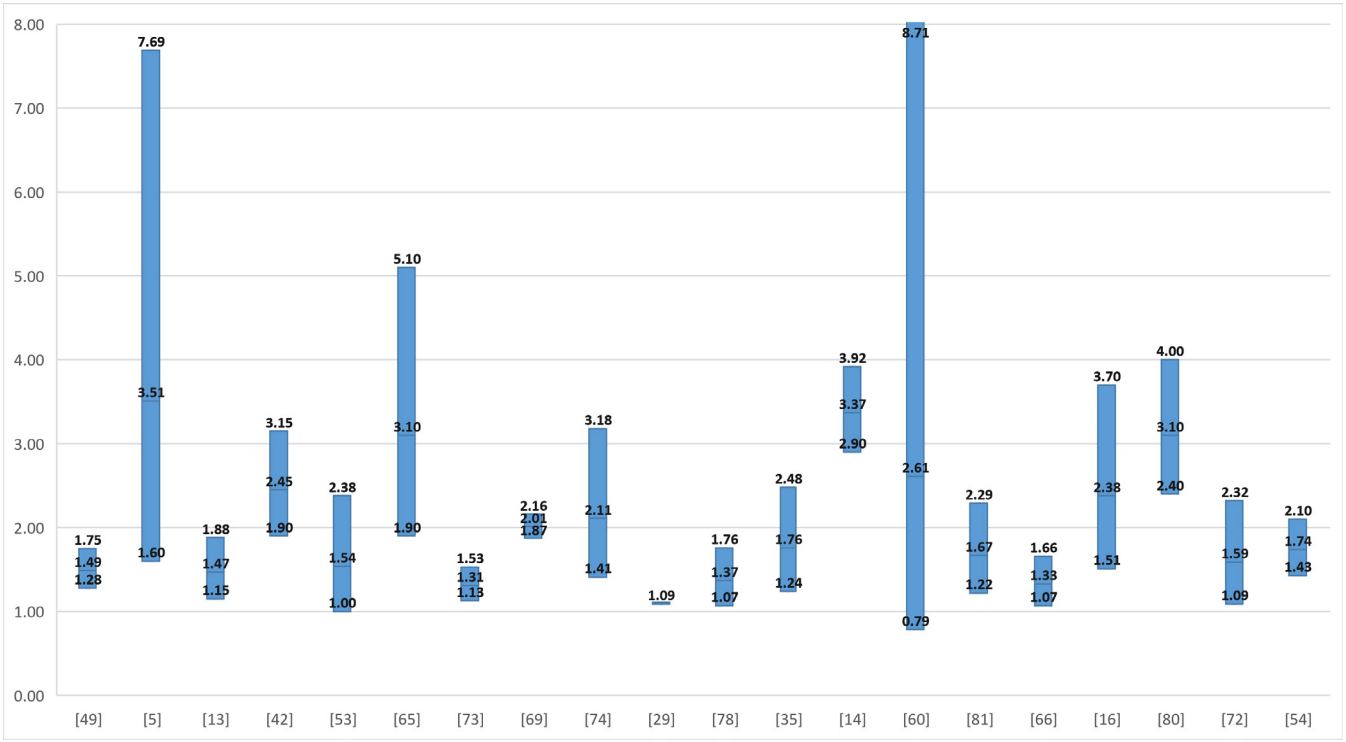


Fig. 1. OR values for severe COVID-19 (including ICU admission) in patients with obesity.

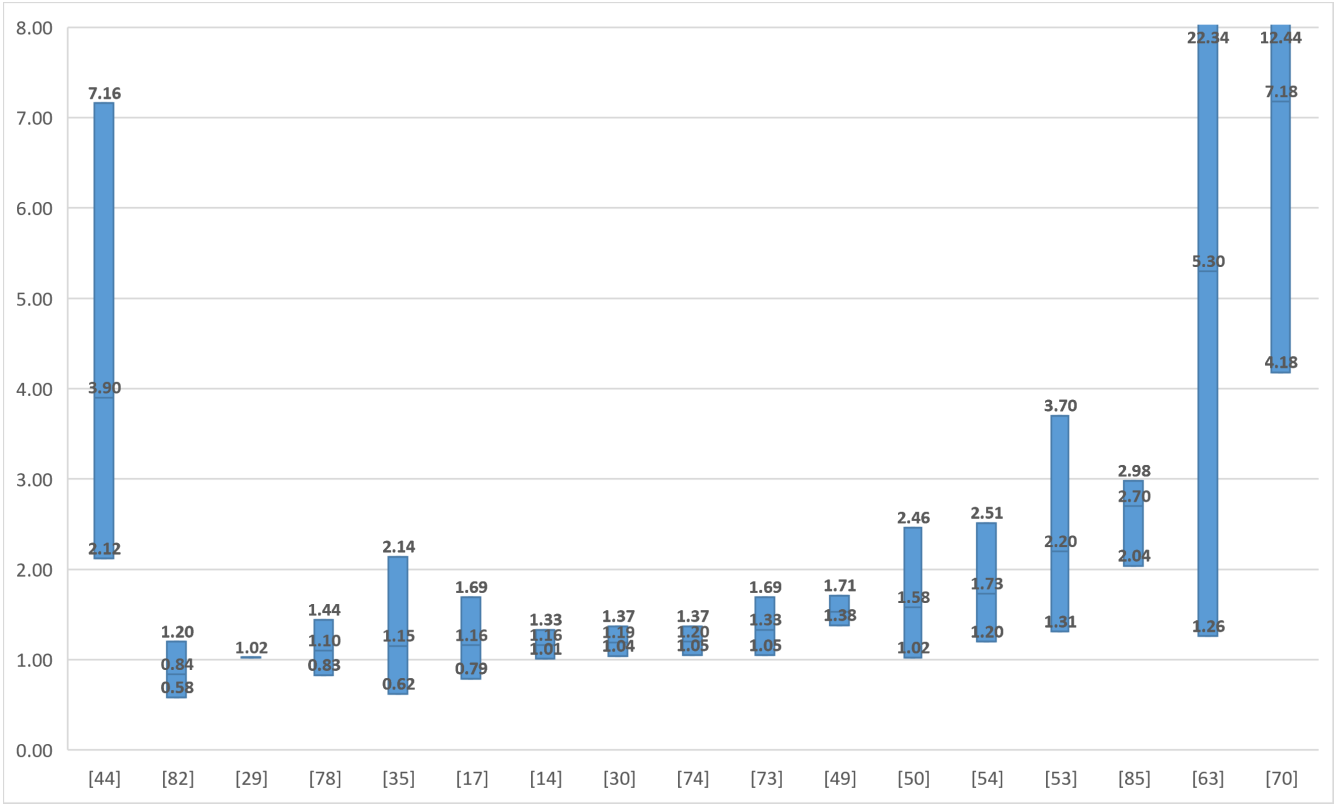


Fig. 2. OR values for in-hospital mortality in patients with obesity.

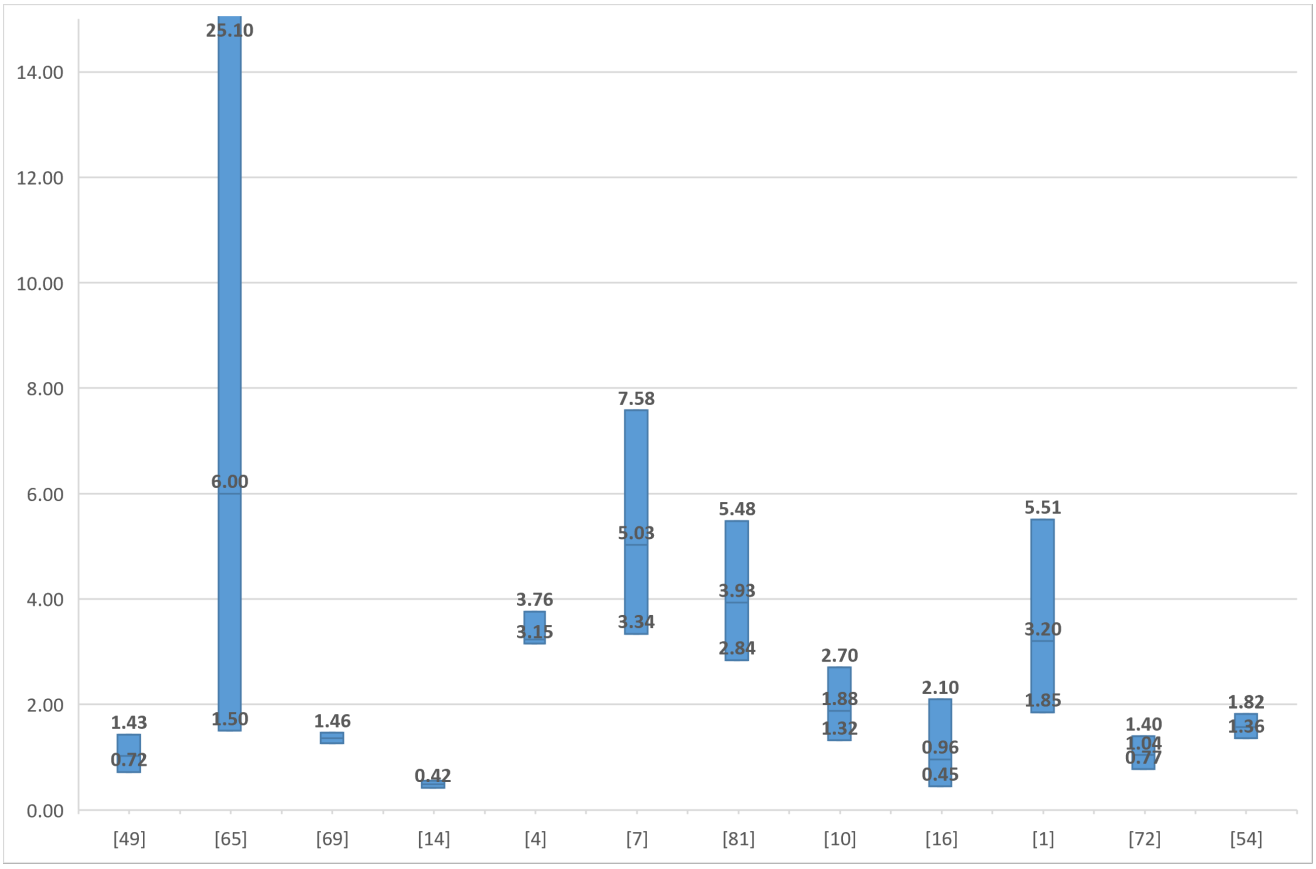


Fig. 3. OR values for severe COVID-19 (including ICU admission) in patients with CVD.

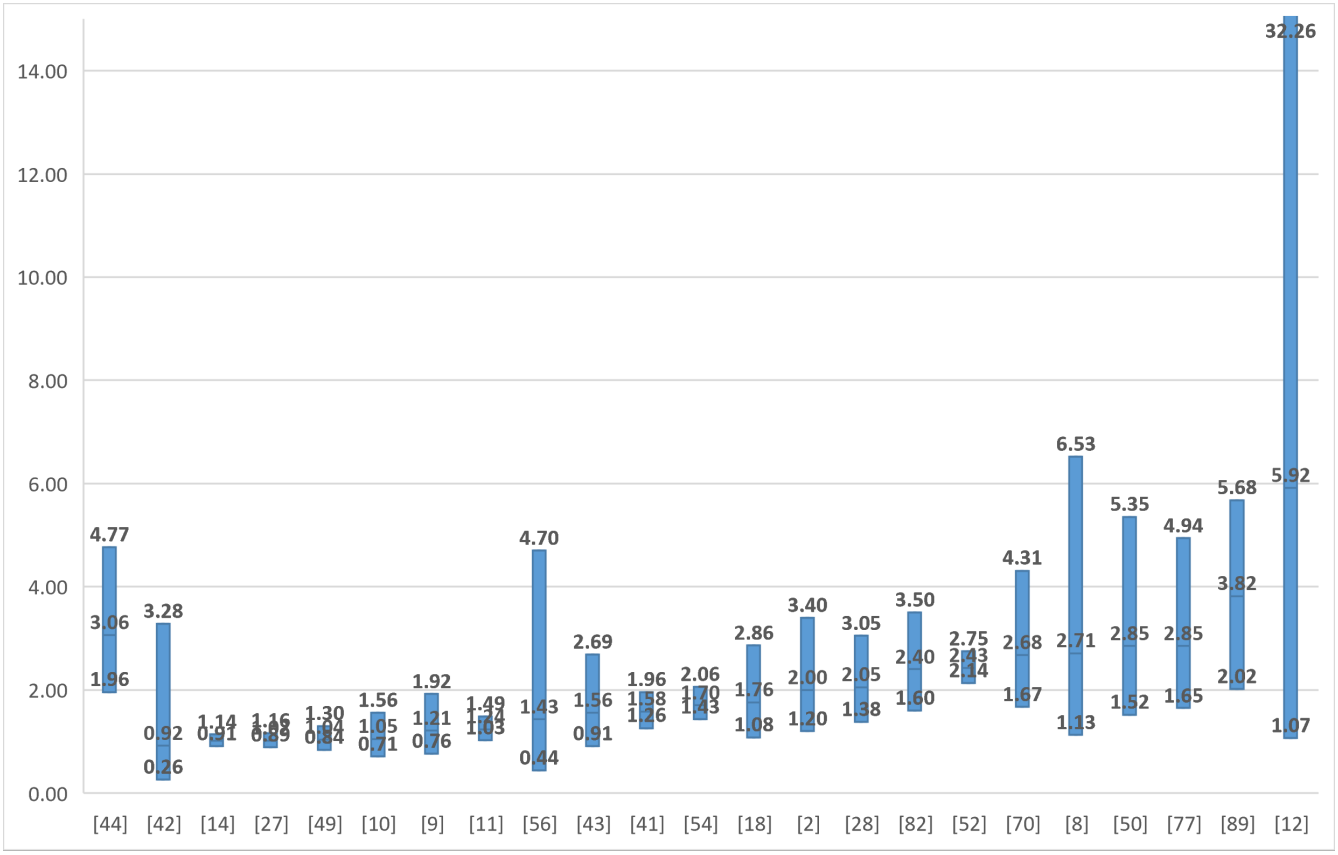


Fig. 4. OR values for in-hospital mortality in patients with CVD.

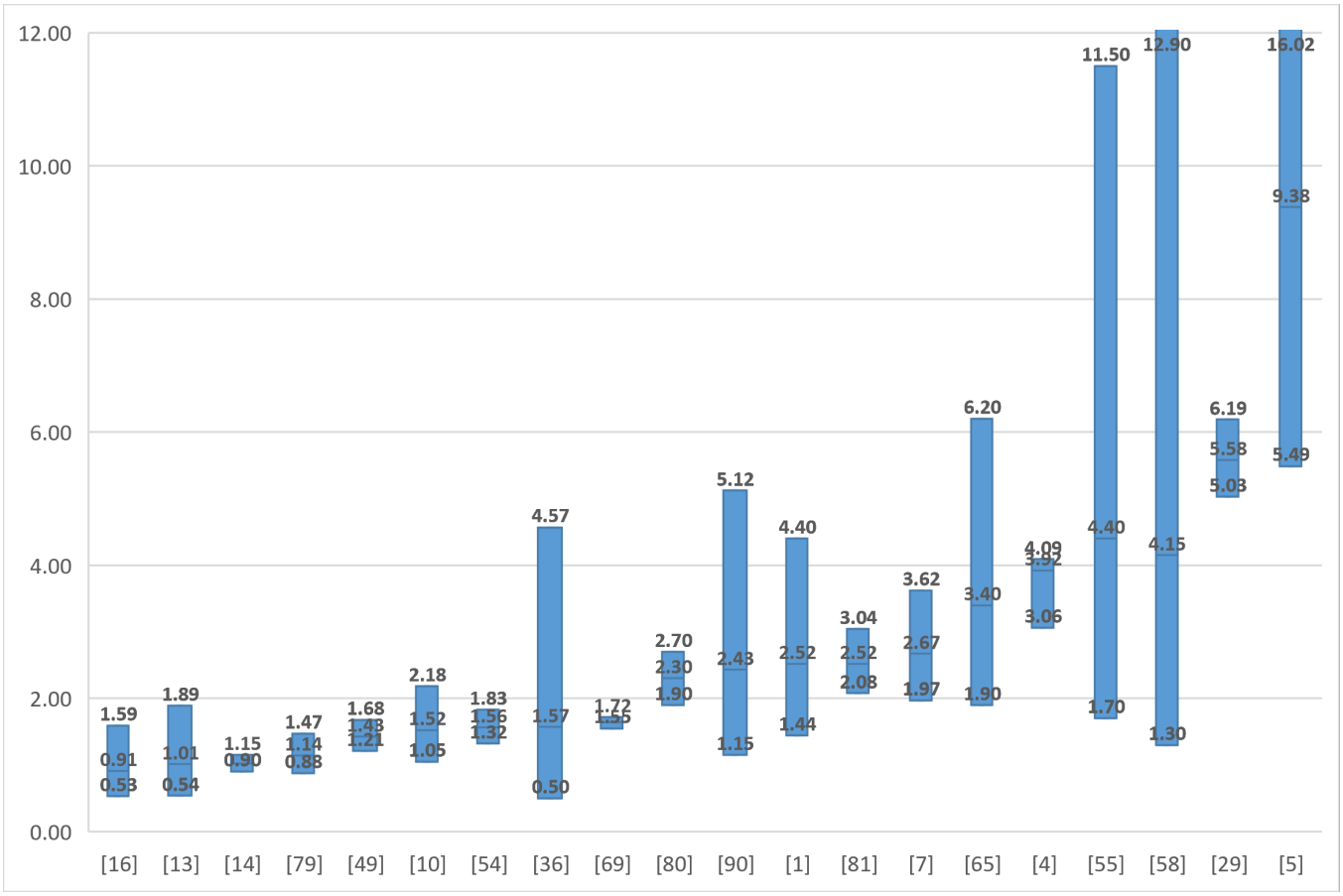


Fig. 5. OR values for severe COVID-19 (including ICU admission) in patients with diabetes.

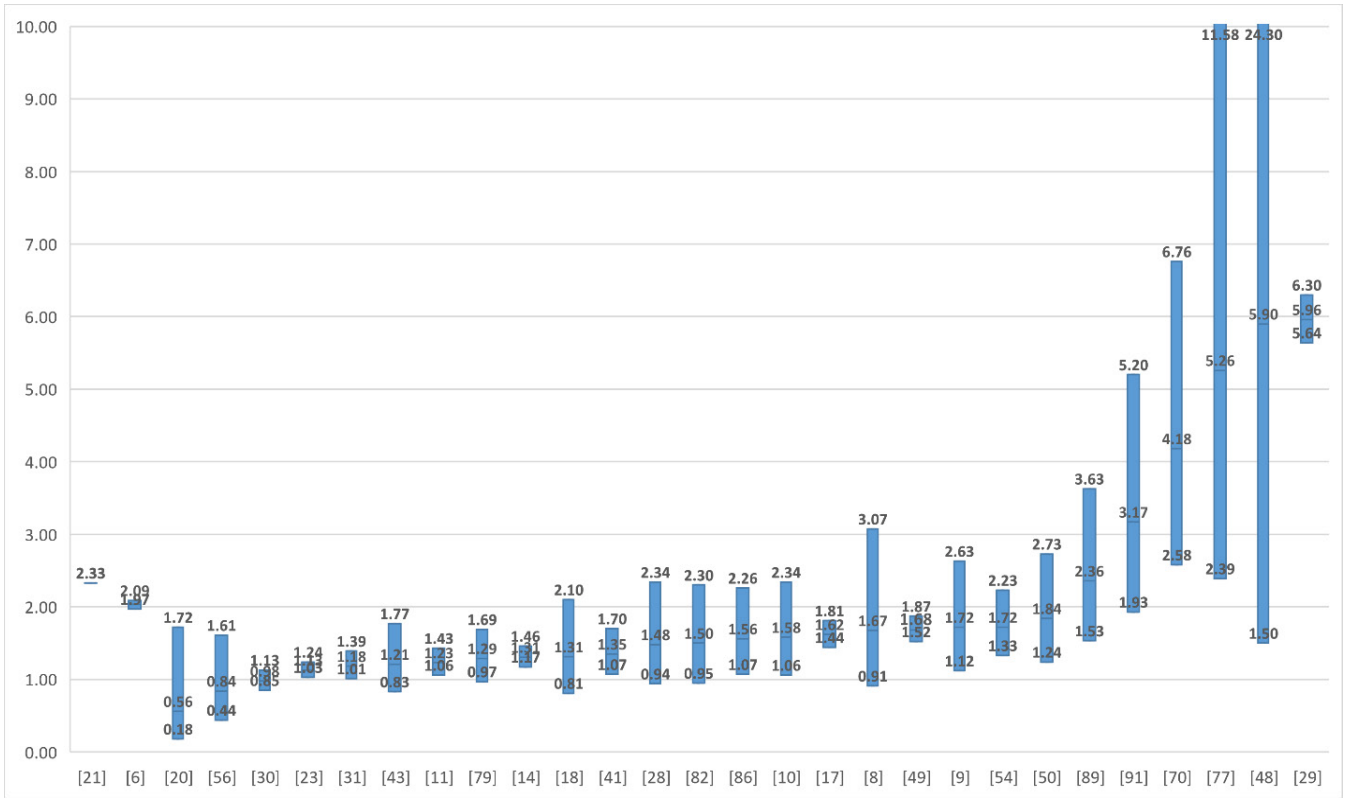


Fig. 6. OR values for in-hospital mortality in patients with diabetes.

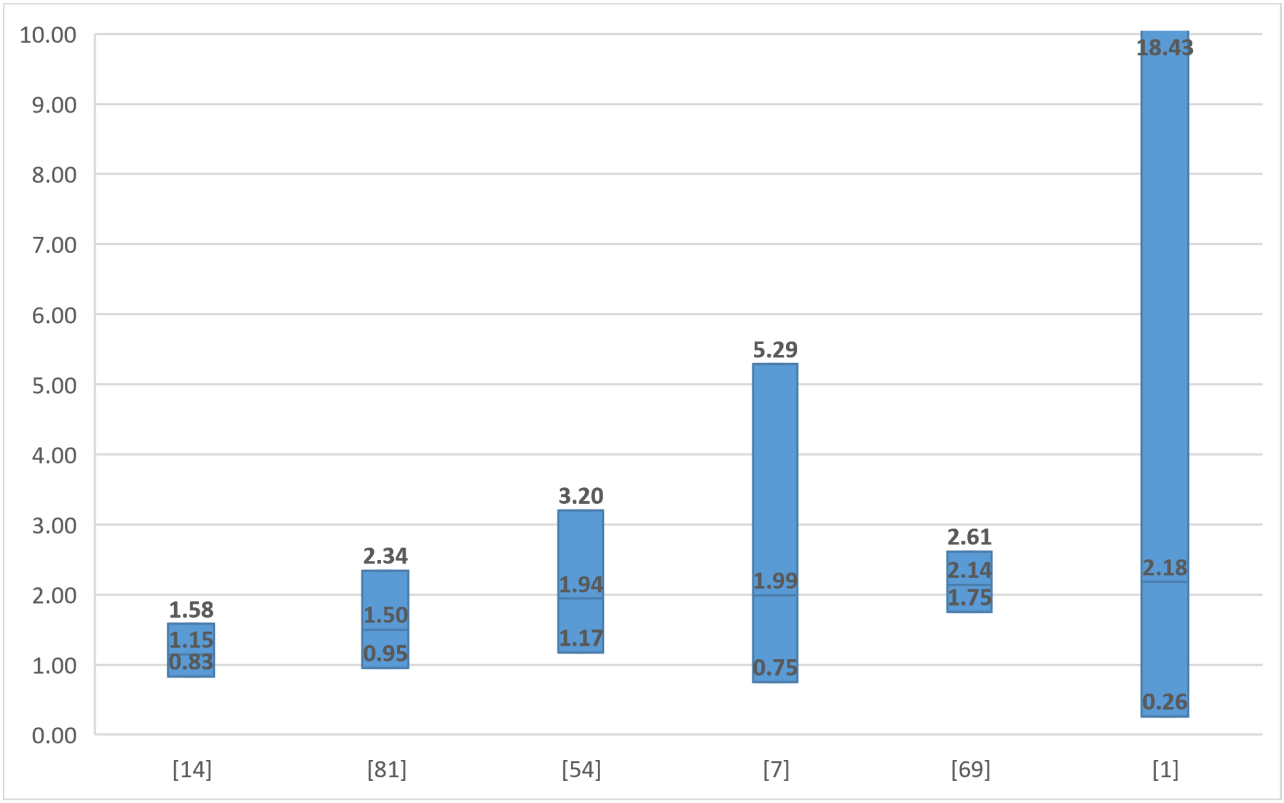


Fig. 7. OR values for severe COVID-19 (including ICU admission) in patients with LD.

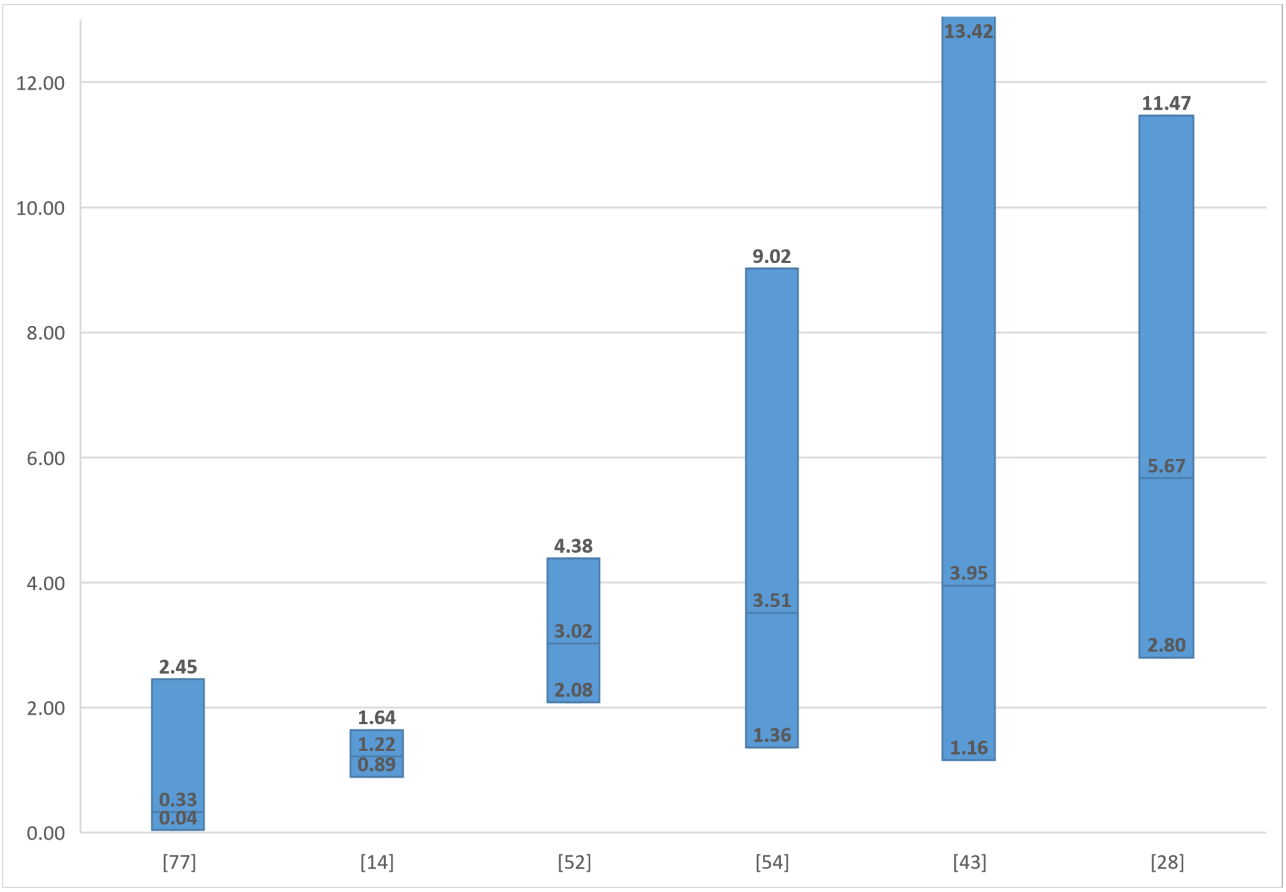


Fig. 8. OR values for in-hospital mortality in patients with LD.

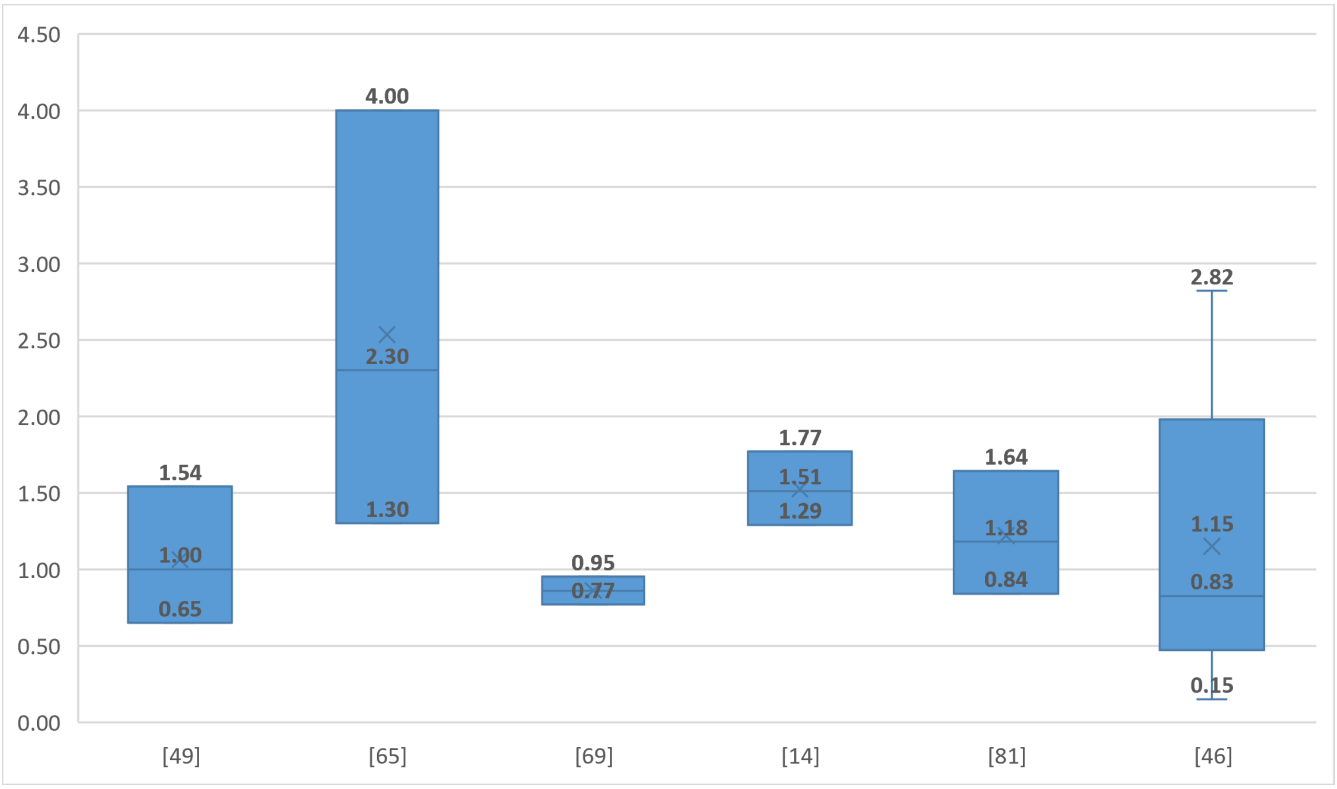


Fig. 9. OR values for severe COVID-19 (including ICU admission) in patients with asthma.

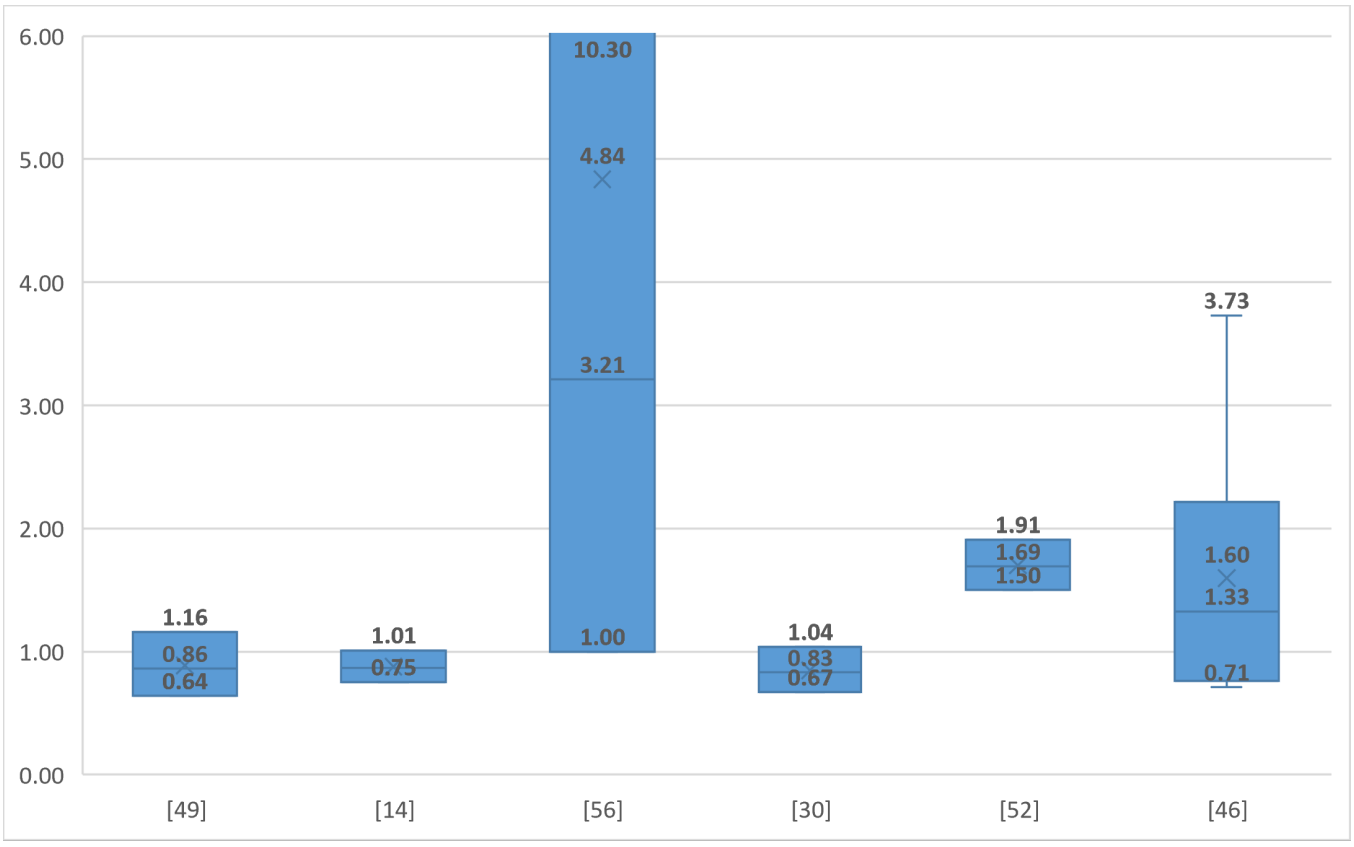


Fig. 10. OR values for in-hospital mortality in patients with asthma.

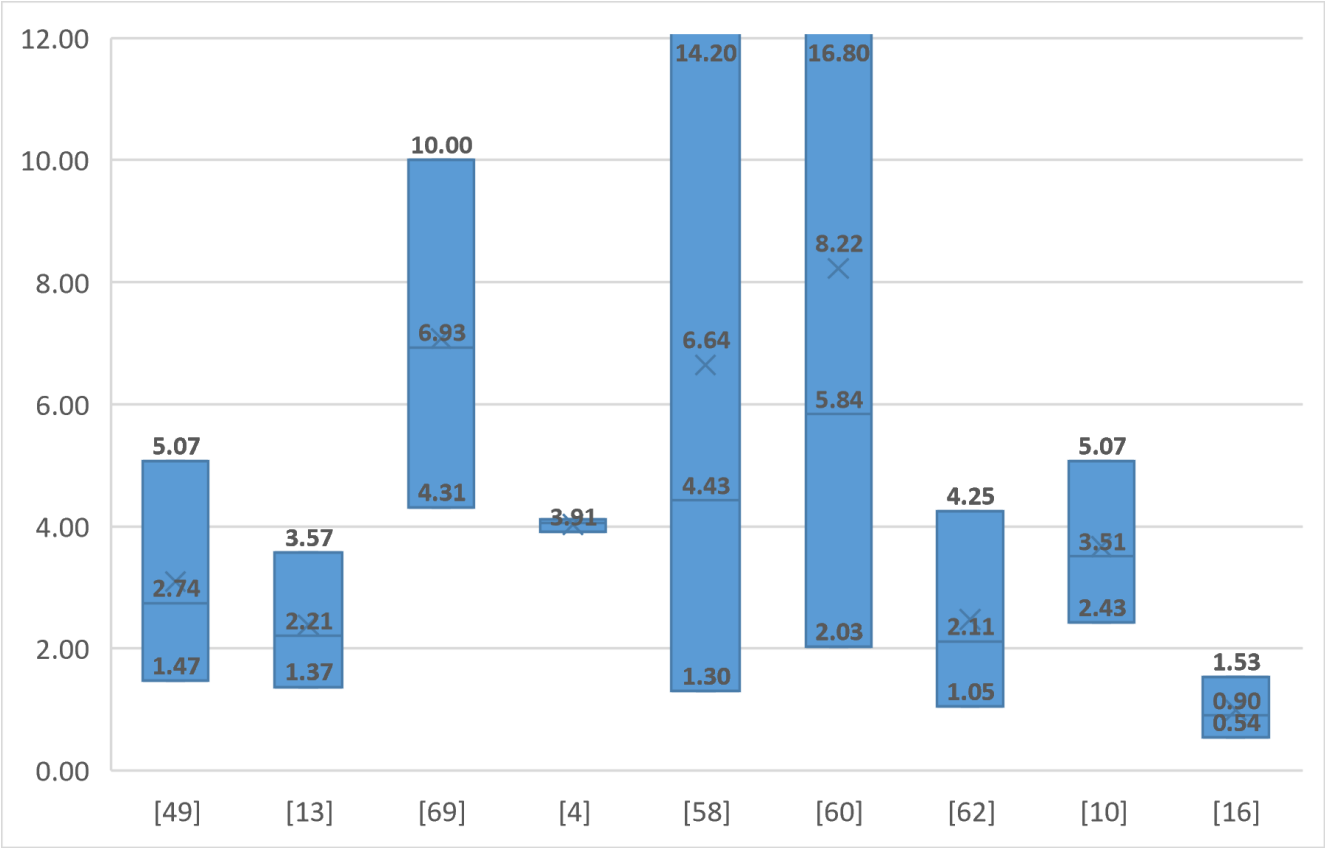


Fig. 11. OR values for severe COVID-19 (including ICU admission) in patients aged 61+.

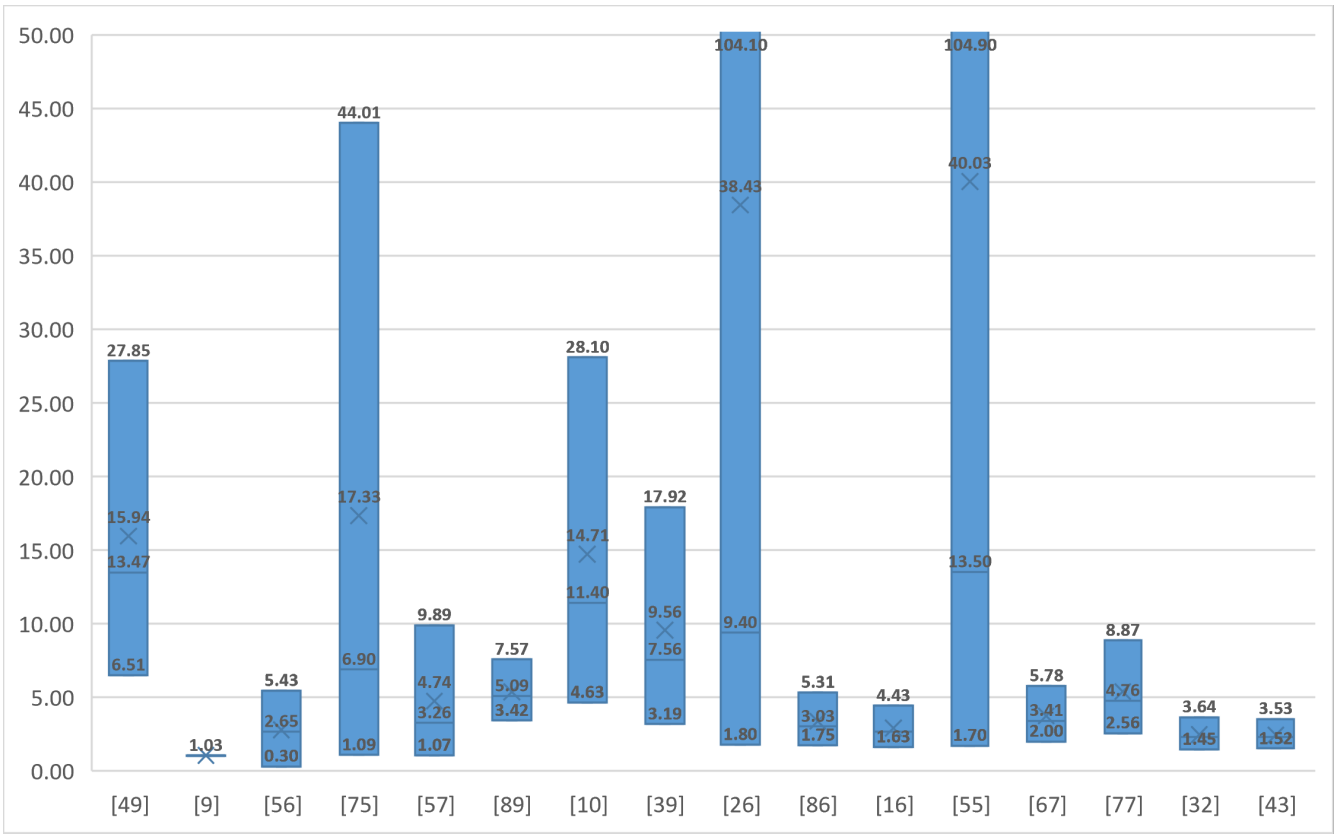


Fig. 12. OR values for in-hospital mortality in patients aged 61+.

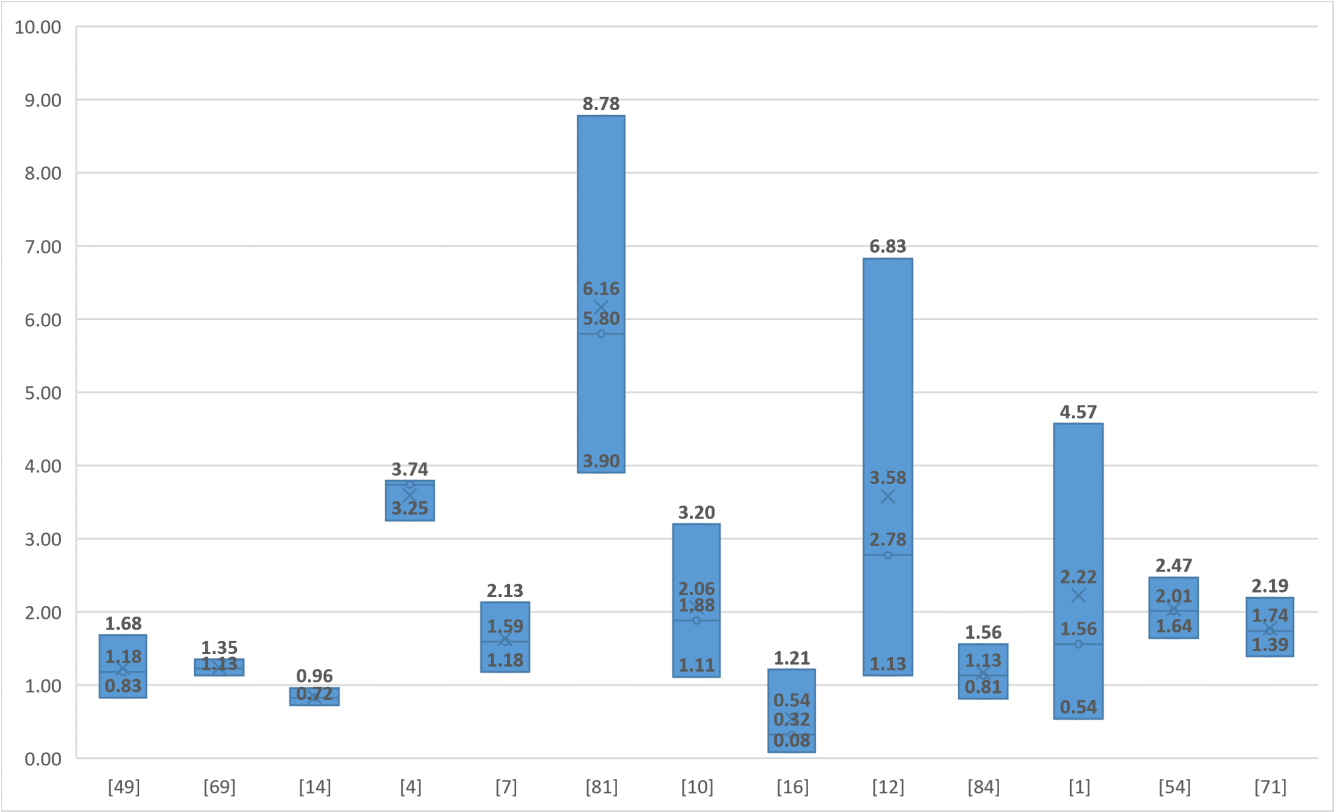
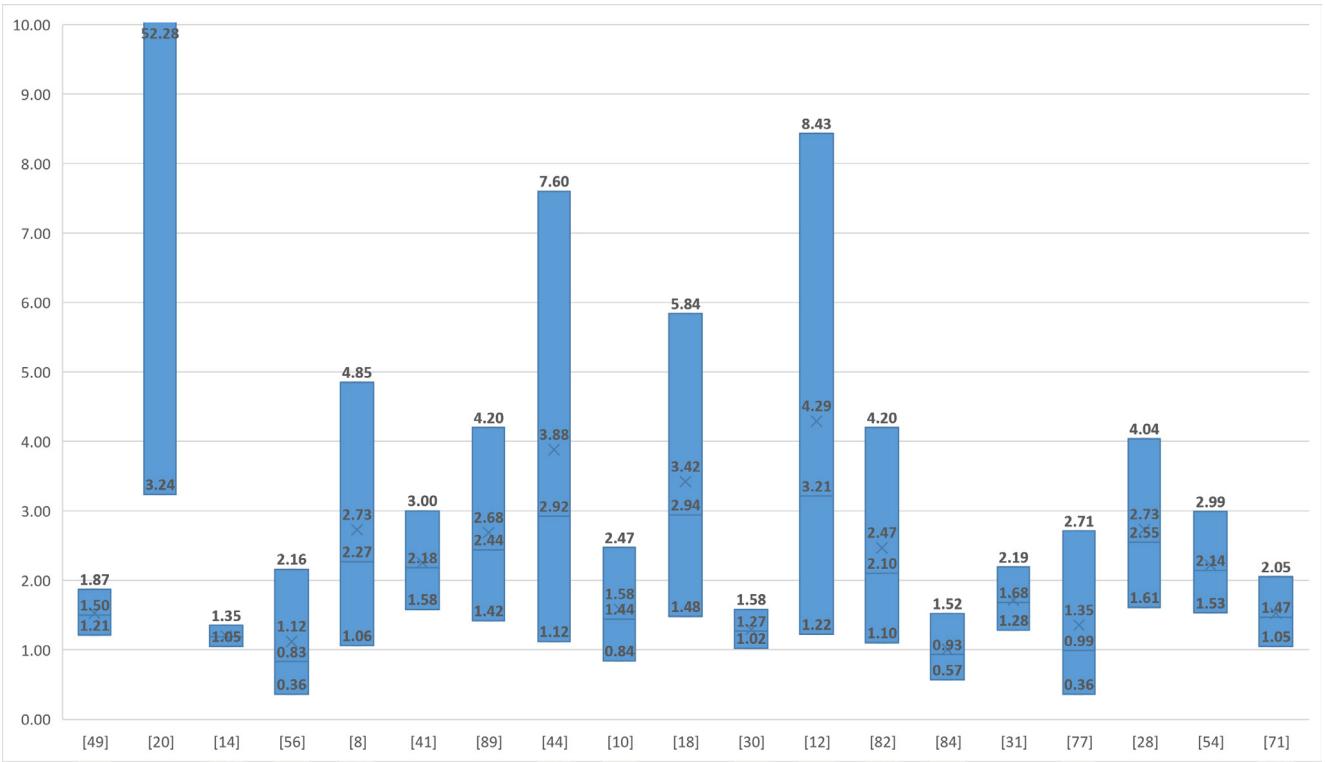


Fig. 13. OR values for severe COVID-19 (including ICU admission) in patients with COPD.



Fig, 14. OR values for in-hospital mortality in patients with COPD.

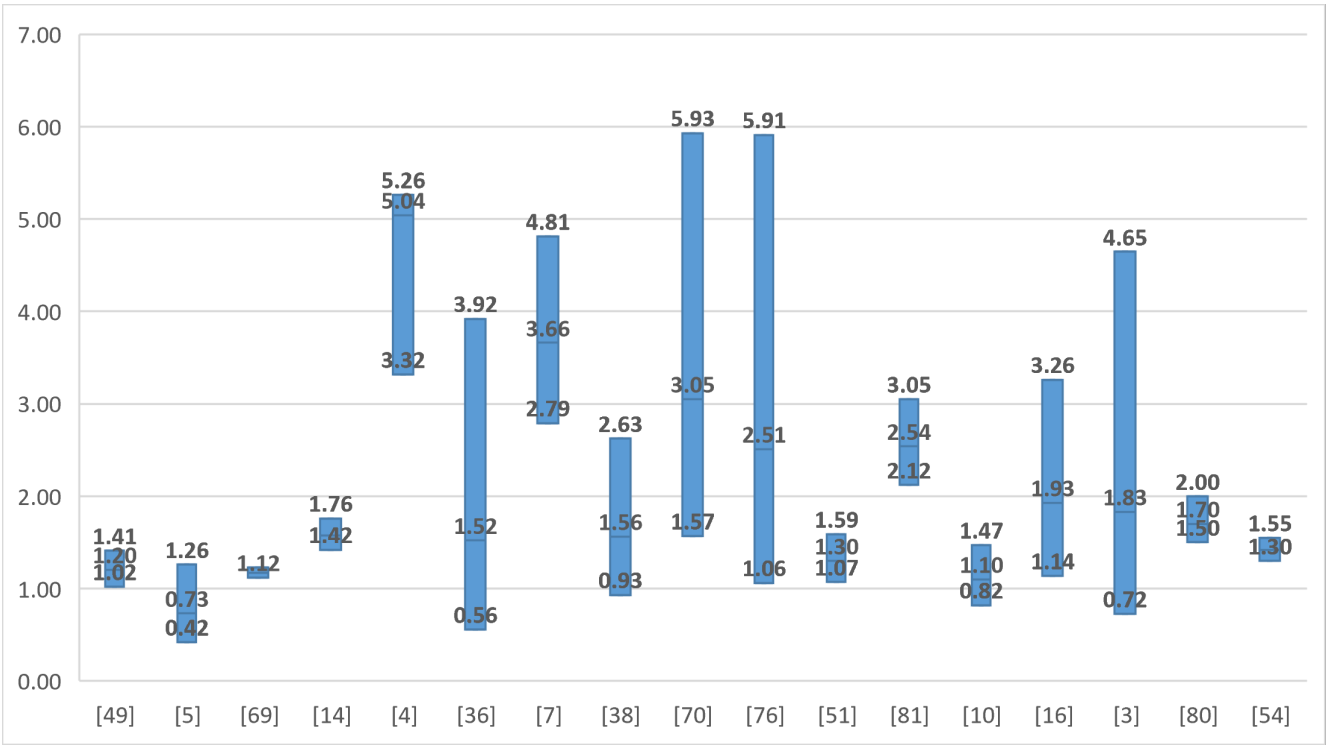


Fig. 15. OR values for severe COVID-19 (including ICU admission) in patients with hypertension.

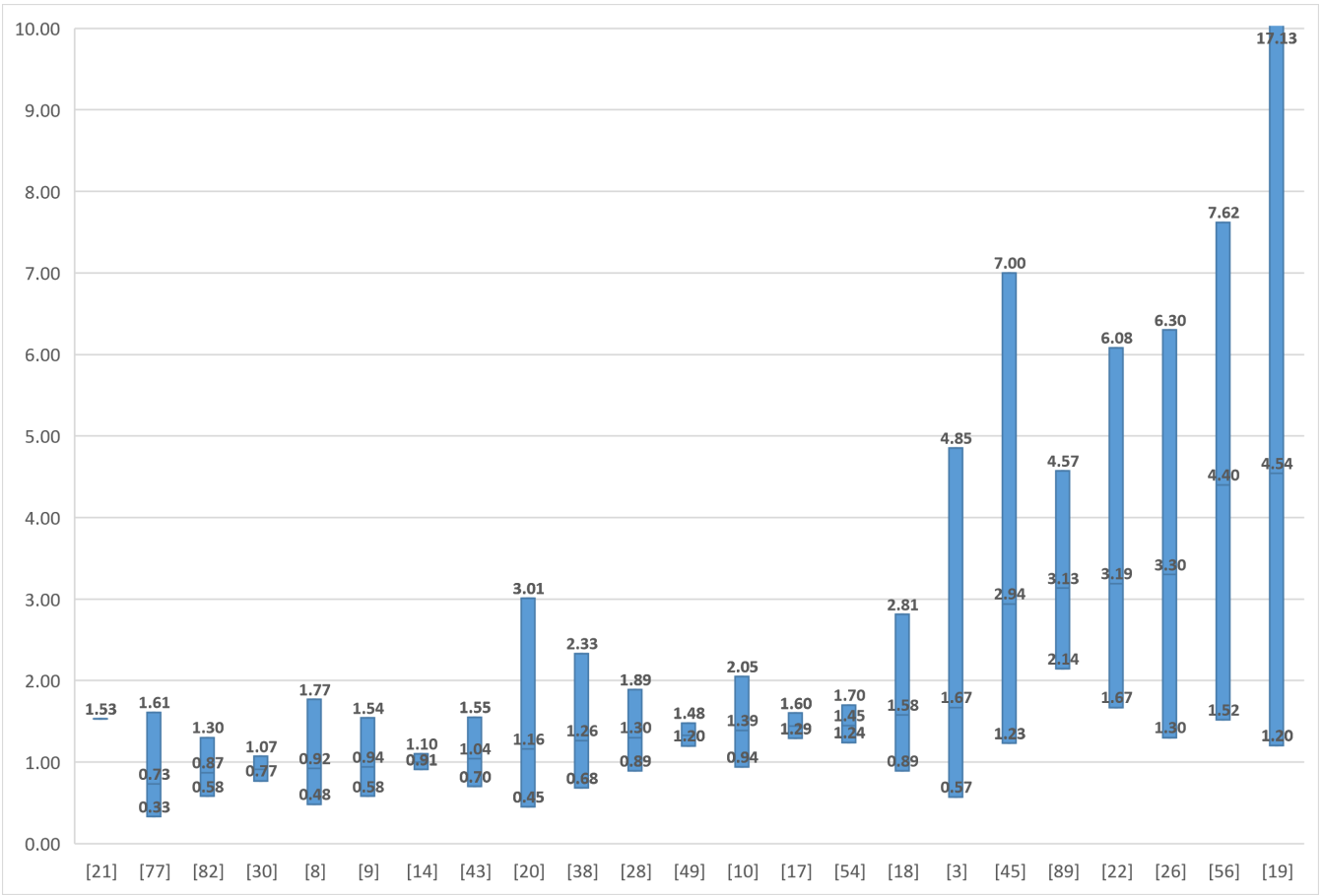


Fig. 16. OR values for in-hospital mortality in patients with hypertension.

Upon further analysis the median OR value of severe disease for obesity was 1.76 (standard deviation (SD) - 1.433), for CVD - 1.7 (SD - 4.182), for diabetes - 1.9 (SD - 2.993), for LD - 1.84 (SD - 4.064), for asthma - 1.18 (SD - 0.861), for age higher than 61 - 3.57 (SD - 3.865), for COPD - 1.56 (SD - 1.82), for hypertension - 1.56 (SD - 1.414) (fig. 17).

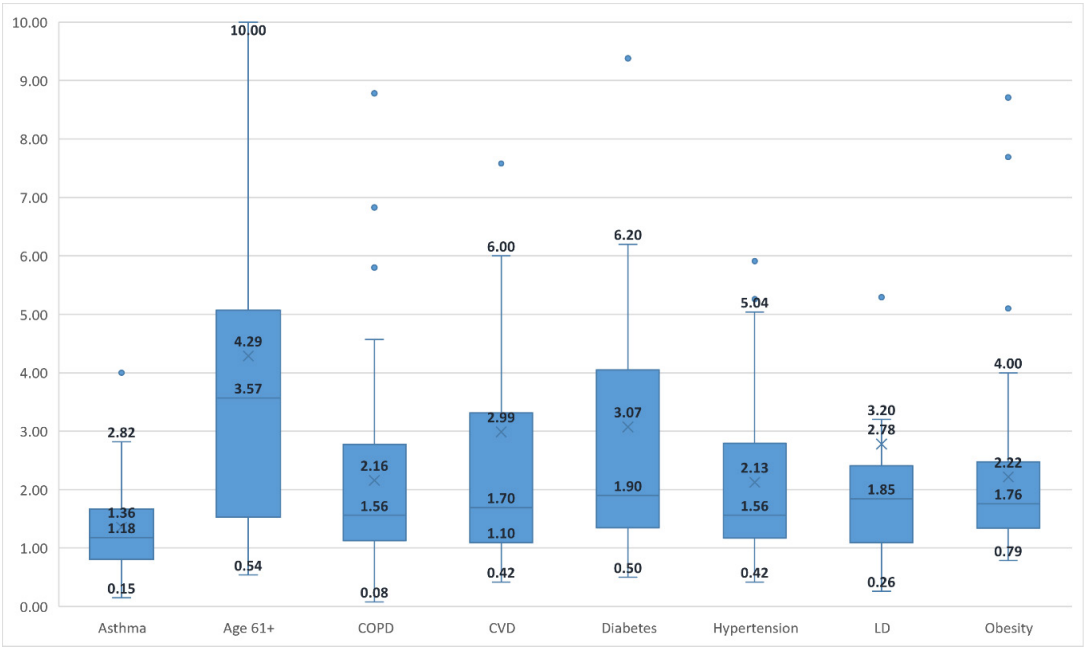


Fig. 17. Cumulative OR values for severe COVID-19 (including ICU admission).
X - mean value; line inside the box - represents the median value.

The median OR value of in-hospital mortality for obesity was 1.37 (SD - 3.5), for CVD - 1.67 (SD - 3.88), for diabetes - 1.61 (SD - 2.92), for LD - 2.63 (SD - 3.82), for asthma - 1.04 (SD - 2.12), for age higher than 61 - 3.58 (SD - 21.39), for COPD - 1.61 (SD - 6.94), for hypertension - 1.44 (SD - 2.41) (fig. 18).

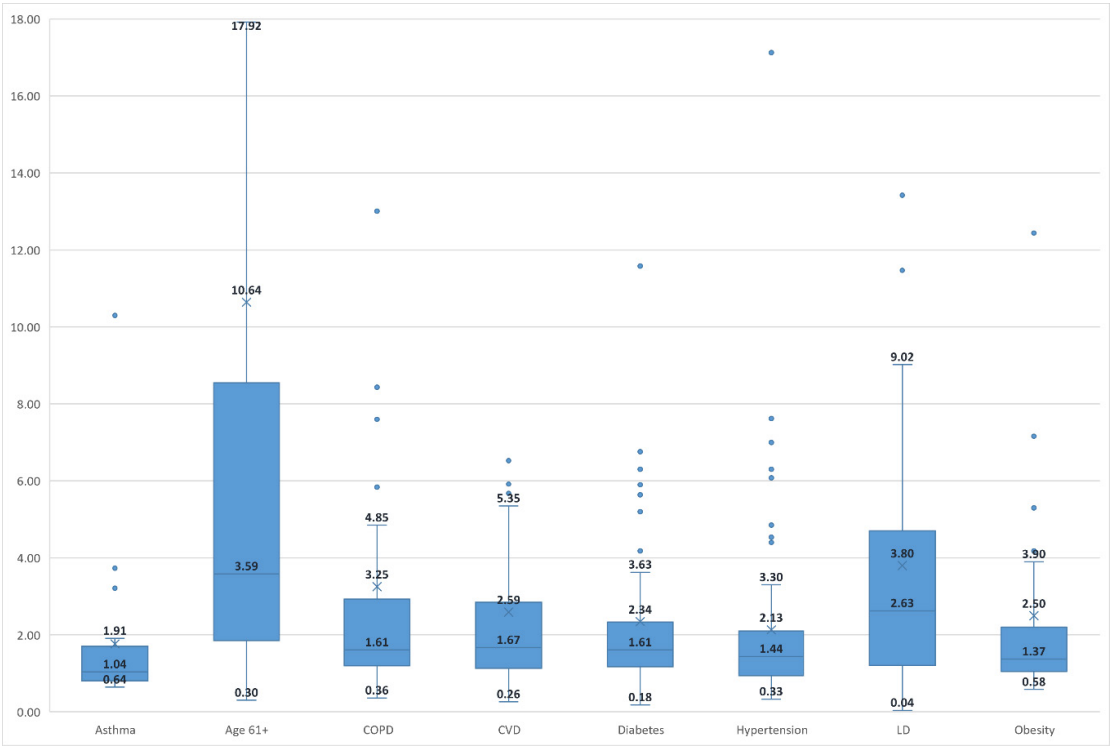


Fig. 18. Cumulative OR values for in-hospital mortality.
X - mean value; line inside the box - represents the median value.

Patients aged 61 years old and higher had the highest risk of in-hospital mortality, as well as transfer to the ICU during in-patient care (OR - 3.58 and 3.57 respectively). Many studies calculate the risk factor for age without dividing the patients into age groups, but rather by establishing a baseline OR which increases with each year of life. But the current consensus is that patients older than 61 years old are at higher risk of severe infection and poor clinical outcomes. And the risk is higher the higher the patients age at presentation. This may be due to the fact that older patients often suffer from additional chronic conditions and are more likely to have a decreased immune response and reduced T-cell immunity. Also, frailty and systemic inflammation of low intensity play a significant role in the worsening of symptoms of COVID-19 and other diseases. The combination of these factors should put patients of older age, specifically older than 60, at high priority during initial presentation with COVID-19 [64, 92, 93].

Liver disease had the second highest mortality risk (OR - 2.63), although the risk of transfer to the ICU was lower (OR - 1.84), compared to other factors. This may be due to the fact, that liver disfunction mostly influences the patient's condition during pharmacological treatment. Drug-induced liver damage results in worse outcomes and is harder to fix during COVID-19 treatment. Rapid elevation of AST and ALT limit treatment options for practitioners and may result in death for the patient. Thus, being aware of the patient's poor liver function can provide practitioners with a head start in choosing treatment options to optimize outcomes [24, 87].

Diabetes, chronic cardiovascular diseases, hypertension and obesity are major factors both for disease severity (OR - 1.9, 1.7, 1.56 and 1.76 respectively) and patient mortality (OR - 1.61, 1.67, 1.44 and 1.37 respectively) and should be considered during initial triage and evaluation. These conditions are manageable in an outpatient setting and if poorly controlled can lead to worse outcomes. These conditions are often interconnected and can influence one another, leading to a vicious circle that deteriorates the patient's general state. Often obesity is the main factor, influencing other conditions through perivascular adipose tissue. Excess perivascular adipose tissue leads to hypoxia and low-grade inflammation, while visceral adipose tissue induces insulin resistance leading to the development of type II diabetes. Obesity can also lead to increased amounts of pericardial adipose tissue, which results in higher values of fasting insulin, blood pressure and pro-inflammatory markers. Obesity is widespread, often called ″The second pandemic″ and only worsened during the COVID-19 pandemic due to stress, isolation and lack of physical activity [15, 37, 68].

Regarding COPD and asthma as primarily lung-oriented conditions, the data suggest that they play a less significant role in disease severity (OR - 1.56 and 1.18 respectively) and mortality (OR - 1.61 and 1.04 respectively). Specifically, asthma was associated with a lower COVID-19 severity in previous studies. For instance, a study by Yunqing Liu et al determined that when comparing in-hospital outcomes for patients with COVID-19 and COPD/asthma, patients with asthma had lower mortality rates and sequential organ failure assessment (SOFA) scores compared to patients with isolated COPD. Furthermore, higher eosinophil counts were attributed to better outcomes even in COVID-19 patients with both COPD and asthma. Isolated COPD due to lower oxygenation led to worsening of COVID-19 and higher instances of invasive ventilation. Also, COPD patients have an increased risk of developing community acquired pneumonia and other respiratory illnesses and need to be carefully monitored [47, 59, 61].

Conclusions. Based on the results of our investigation we conclude that comorbid conditions significantly influence the course of COVID-19 in patients and should be taken into consideration during initial evaluation of the patient. In particular, patient`s age and function of liver play a key role during decision making, planning treatment and diagnosis. Based on the analyzed data we conclude that the development of such a score system is possible. Arming primary care physicians with such a score system akin to tools used by hospital doctors, based on widespread chronic conditions can help in triage and medical care. Implementing such a tool into the healthcare system will help alleviate the strain on the healthcare system both during and after the pandemic, as well as help further evaluate the effect of these conditions on other respiratory illnesses and their outcomes.

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Conflict of interest
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Analysis of the Influence of Comorbid States on COVID-19 Severity and In-Hospital Mortality for Further Application in an Outpatient Setting

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Introduction. The COVID-19 pandemic brought many challenges to the healthcare systems of all countries. Primary care physicians were on the front-lines, handling outpatient care, performing triage, consulting patients on potential risks, symptoms of concern and treatments options. And although emergency and intensive care units have been using severity scales like the quick COVID-19 severity index, Brescia-COVID Respiratory Severity Scale to rapid asses patient severity and adjust care accordingly, these metrics only apply for an inpatient setting and don't provide much use for outpatient care and management. By isolating main risk factors for developing severe COVID-19, a tool like this can be created for quick evaluation in an outpatient setting.

The aim of the study. To analyze available research data regarding the most common comorbid conditions of patients with a confirmed COVID-19 infection during in-hospital treatment and their role in disease severity and mortality, and to evaluate the possibility of developing a similar score system for outpatient use.

Materials and methods. Articles on COVID-19 patient care, disease progression, comorbidities and outcomes were gathered from the PubMed using a combination of keywords: COVID-19 (main search keyword), obesity, cardiovascular disease (CVD), hypertension, diabetes, liver disease (LD), asthma, chronic obstructive pulmonary disease (COPD), severity, outcomes. From the register under investigation were excluded articles based on the criteria as follows: patient groups consisting of children under the age of 18 and pregnant women, the lack of calculated odds ratios (OR) and patient groups with high risk underlying conditions without multivariable analysis to exclude interference in the results. The data were analyzed based on two main outcomes for each comorbidity – severe disease (including inpatient ICU transfer) and in hospital mortality.

Results. In total 77 articles were chosen based on the defined criteria. Data about OR for patients with relevant risk factors compared to patients without ones, for severe disease course (including in-hospital ICU admission) and mortality were analyzed for each criterion. For obesity the OR for severe disease spanned from 1.1 to 3.51, for CVD - 1.02 to 6, for diabetes - 0.91 to 9.38, for LD - 1.146 to 2.18, for asthma - 0.66 to 2.3, for patients older than 61 - 0.90 to 6.93, for COPD - 0.32 to 5.80, for hypertension - 0.73 to 5.04. The OR for in-hospital mortality were as follows: obesity - 0.84 to 7.18, CVD - 0.92 to 5.917, diabetes - 0.56 to 5.96, LD - 0.33 to 5.67, asthma - 0.83 to

3.21, patients older than 61 - 1.05 to 13.5, COPD - 0.83 to 13.01, hypertension - 0.73 to 4.54. Upon further analysis the median OR value of severe disease for obesity was 1.76, for CVD - 1.7, for diabetes - 1.9, for LD - 1.84, for asthma - 1.18, for age higher than 61 - 3.57, for COPD - 1.56, for hypertension - 1.56. The median OR value of in-hospital mortality for obesity was 1.37, for CVD - 1.67, for diabetes - 1.61, for LD - 2.63, for asthma - 1.04, for age higher than 61 - 3.58, for COPD - 1.61, for hypertension - 1.44.

Conclusions. Comorbid conditions have significant influence on the course of COVID-19 in patients and should be taken into consideration during initial evaluation of the patient`s status. In particular, age and liver function play a key role during decision making, planning treatment and diagnosis. Development and implementation of a tool akin to inpatient scores into the healthcare system will help alleviate the strain on the healthcare system both during and after the pandemic.

Keywords: COVID-19, scale, comorbidities, outpatient setting, outcomes.

Аналіз впливу коморбідних станів на тяжкість COVID-19 і лікарняну смертність для подальшого прикладного використання в амбулаторних умовах

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Вступ. Пандемія COVID-19 створила багато викликів для систем охорони здоров'я усіх країн. Лікарі загальної практики здійснювали амбулаторний догляд, сортування, консультування пацієнтів щодо потенційних ризиків, тривожних симптомів і варіянтів лікування. І хоча відділи невідкладної допомоги та інтенсивної терапії застосовували шкали оцінювання тяжкости захворювання на кшталт швидкісного індексу тяжкости COVID-19 і Брешської шкали оцінювання тяжкости легеневих виявів COVID для швидкого оцінювання тяжкости стану пацієнта, ці шкали придатні лише для використання під час шпиталізації, а не під час амбулаторного догляду. Якщо ізолювати основні чинники ризику наростання тяжкости COVID-19, можна створити подібний інструмент для швидкого оцінювання на амбулаторному етапі.

Мета. Проаналізувати наявні дослідження щодо найпоширеніших коморбідних станів у пацієнтів із підтвердженою інфекцією COVID-19 під час шпиталізації та їхній вплив на тяжкість хвороби і летальність. Оцінити можливість створення шкали, придатної для використання на амбулаторному етапі.

Матеріяли й методи. Дослідження щодо догляду за пацієнтами з COVID-19, перебігу хвороби, коморбідних станів і результатів лікування були зібрані з PubMed за ключовими словами: COVID-19 (основне), ожиріння, серцево-судинні хвороби (ССХ), гіпертензія, діябет, хвороби печінки (ХП), астма, хронічна обструктивна хвороба легень (ХОХЛ), тяжкість, результати. Статті виключали з пошуку за такими критеріями: групи пацієнтів віком менше 18 років і вагітні жінки, відсутність визначеного відносного ризику (ВР) та наявности груп пацієнтів із супутніми станами високого ризику без проведення мультиваріябельного аналізу з метою уникнути впливу на результати.

Аналіз здійснювали за двома основними результатами щодо кожної коморбідности – тяжкий перебіг хвороби (включно з переведенням до відділу інтенсивної терапії) і лікарняна смертність.

Результати. Відібрано 77 досліджень згідно з визначеними критеріями.

Інформацію щодо ВР для пацієнтів із обраними чинниками ризику порівняно з пацієнтами без них для тяжкого перебігу хвороби (включно з переведенням до відділу інтенсивної терапії) і смертности аналізували для кожного критерію. Для ожиріння показники ВР для тяжкого перебігу хвороби становили від 1,10 до 3,51, для ССХ – від 1,02 до 6,00, для діябету – від 0,91 до 9,38, для ХП – від 1,146 до 2,180, для астми – від 0,66 до 2,30, для пацієнтів віком понад 61 рік – від 0,90 до 6,93, для ХОХЛ – від 0,32 до 5,80, для гіпертензії – від 0,73 до 5,04.

Показники ВР для лікарняної смертности такі: ожиріння – від 0,84 до 7,18, ССХ – від 0,920 до 5,917, діябету – від 0,56 до 5,96, ХП – від 0,33 до 5,67, астми – від 0,83 до 3,21, пацієнтів віком понад 61 рік – від 1,05 до 13,50, ХОХЛ – від 0,83 до 13,01, гіпертензії – від 0,73 до 4,54.

Аналіз медіян ВР для тяжкого перебігу хвороби показав для ожиріння 1,76, для ССХ – 1,70, для діябету – 1,90, для ХП – 1,84, для астми – 1,18, для пацієнтів віком понад 61 рік – 3,57, для ХОХЛ – 1,56, для гіпертензії – 1,56.

Показники медіяни ВР для лікарняної смертности становили для ожиріння 1,37, для ССХ – 1,67, для діябету – 1,61, для ХП – 2,63, для астми – 1,04, для пацієнтів віком понад 61 рік – 3,58, для ХОХЛ – 1,61, для гіпертензії – 1,44.

Висновки. Згідно з нашими дослідженнями, супутні стани можуть впливати на перебіг COVID-19, їх варто брати до уваги під час первинного оцінювання стану пацієнта. Вік і функція печінки особливо важливі під час прийняття рішень, планування лікування та діягностики. Розроблення і впровадження у систему охорони здоров'я інструменту, подібного до лікарняних шкал, уможливить зняти навантаження з системи охорони здоров'я під час пандемії та за її межами.

Ключові слова: COVID-19, шкала, коморбідність, амбулаторні умови, результати.

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