



Out-of-pocket expenditures in hospitalized COVID-19 patients: A systematic review and meta-analysis

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Abstract:

The outbreak of COVID-19 has led to substantial out-of-pocket (OOP) expenditures for households during treatment. This study aimed to investigate the OOP expenditures among hospitalized patients with COVID-19 through a systematic review and meta-analysis. A systematic review and meta-analysis were conducted following the PRISMA guidelines. Articles were retrieved from the PubMed, Scopus, and Google Scholar in the period of 2019–2022 and evaluated for quality using the STROBE guidelines. Homogeneity was assessed using the I² index, and publication bias was examined using a funnel plot. Meta-analysis was performed using Stata 16. Results of the study have shown that a total of nine articles were included in the meta-analysis. The average OOP expenditure for hospitalized COVID-19 patients was found to be US \$308.25 (95% CI: 4.17-620.67). The highest OOP expenditure was reported by CHAU (2021) (US \$3171.28), followed by GRAG (2022) (US \$1582.38), and the lowest by KOTWANI (2021) (US \$56.35). According to the results obtained Significant inequality was observed in the OOP expenditures across different countries. Consistent policy recommendations should be made in international forums to reduce these costs in future pandemics for patients in both developed and developing nations.

Keywords:

COVID-19, health expenditures, meta-analysis, systematic review

Introduction

In December 2019, there was an outbreak of respiratory disease of unknown cause in Wuhan, China. The causative agent of this severe acute respiratory syndrome is coronavirus. This acute respiratory syndrome is known as COVID-19.^[1,2] On March 16, 2020, the COVID-19 outbreak and coronavirus cases have been reported by more than 151 countries.^[3] Globally, on 30 January, the WHO declared an international public health emergency and called on all countries to make cooperative efforts to prevent the rapid spread of coronavirus disease 2019 (COVID-19).^[4]

The outbreak of the coronavirus disease 2019 (COVID-19) has rapidly unfolded,

bringing about numerous unforeseen changes in the well-being of individuals at national and global levels. Consequently, it has directly and indirectly disrupted various socioeconomic aspects within communities.^[5] As the pandemic spread, it became increasingly evident that vulnerable populations were disproportionately affected. These disparities can be attributed to the intertwining of health and economic inequalities. This is not a new phenomenon, as evidenced by the significant impact of the 2009 influenza epidemic on 20% of the poorest population in England, as well as the notably higher mortality rates observed in certain South American countries compared to European nations. The outbreak of COVID-19 has further emphasized the

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Received: 29-08-2023

Accepted: 28-10-2023

Published: 28-10-2024

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How to cite this article: Ahmadabad AD, Hosseini_Shokouh SM, Mehdizadeh P, Meskarpour_Amiri M. Out-of-pocket expenditures in hospitalized COVID-19 patients: A systematic review and meta-analysis. J Edu Health Promot 2024;13:404.

association between socioeconomic indicators, including income, social class, work experience, and educational progress, and health outcomes. Specifically, individuals with lower socioeconomic status tend to have higher rates of underlying diseases, such as heart diseases, which not only lead to weaker treatment outcomes but also result in higher costs.^[6]

Globally, the pandemic has affected millions of people, causing illness and death, prompting policymakers to reevaluate various standard policies, and including the allocation of healthcare costs between health insurance and out-of-pocket (OOP) expenditures. In the absence of health insurance, households faced with significant medical expenses may encounter severe financial challenges. Conversely, if insurance companies fully reimburse these costs, moral hazards can arise, leading individuals to disregard potential risks since all expenses are covered by insurance. The optimal approach lies in finding a balance, where the proportion of costs covered by insurance ranges from 0% to 100%. As COVID-19 continues to afflict millions of people, the percentage of OOP expenditures has escalated, compelling households to tap into their income sources.^[7]

In conclusion, out-of-pocket (OOP) expenditures have a profound impact on household finances and overall well-being. High OOP expenditures for healthcare services can lead to catastrophic health expenditures (CHEs) and contribute to existing disparities in healthcare financing.^[8]

Today, the lack of financial protection in health is known as a disease of health systems. The clearest sign of this is that households suffer not only from the burden of disease, but also from the burden of destruction and economic poverty, in other words, facing back-breaking costs in their health system.^[9] Therefore, it is not surprising that the concern regarding the costs of people's health, nowadays it attracts the attention of policymakers and academics. However, the World Health Organization considers the protection of people against the costs of diseases as one of its three main goals. The health system has determined. Paying from patients' pockets is one of the simplest and at the same time the least effective methods of payment. Despite the problems, this method has allocated a large volume of payments. The use of direct payments as a supplement to tax credits and a source of support for organizations providing health services will be useful. Except for very rich people, there is doubt.^[10]

Examining the economic burden of diseases and out-of-pocket costs has attracted a lot of attention in recent years.^[11] Paying attention to the volume of direct out-of-pocket payments by households is an important factor that should always be considered in calculations related

to planning and policymaking. Health services should be considered.^[12] Due to the fact that not much time has passed since the outbreak of COVID-19, a few studies have investigated the rate of out-of-pocket payments among patients with this disease, and the conducted studies have also presented different results in this field, as well as a study that a systematic review of existing studies in this field has not been done.

Considering the fact that out-of-pocket healthcare costs have a great impact on the health system of countries and individuals and are considered a very important phenomenon in the health system, in order to summarize and achieve a reliable result in the field of out-of-pocket payment in COVID-19 patients, this study has done a systematic review and meta-analysis of the amount of out-of-pocket payments in hospitalized COVID-19 patients.

The results of this study can show health policymakers and planners, the status of out-of-pocket payments among patients with COVID-19, so that they can evaluate their decisions and policies accordingly. Also, these results help them plan and make better decisions in order to reduce out-of-pocket costs.

Materials and Methods

This systematic review and meta-analysis utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and encompassed the following steps:

Search strategy

Initially, articles published in journals indexed in the PubMed and Scopus databases were retrieved. Additional studies were obtained through manual searches conducted on Google Scholar. The search employed relevant keywords and appropriate operators, while incorporating specific limitations such as the English language and the publication period from 2019 to 2021 (PubMed) and 2019 to 2022 (Scopus and Google Scholar). The results of this search are presented in Table 1.

Article selection

Initially, a directory comprising the titles and abstracts of all retrieved articles was created. Duplicate titles were identified and excluded, followed by a review of the remaining abstracts to identify more suitable studies. The primary inclusion criterion was studies focusing on the out-of-pocket (OOP) expenditures among patients hospitalized with COVID-19. To ensure sensitivity in article selection and identify the most relevant and high-quality studies, exclusion criteria were applied. These included studies that were irrelevant in terms

of research design and topic, those with inadequate information about OOP expenditures, lacking measures of dispersion, and low-quality articles as assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The flow diagram in Figure 1 presents the selection process for articles included in this systematic review and meta-analysis. Initially, a total of 67 articles were retrieved from Scopus and 11 from PubMed databases. Additionally, three studies were obtained through manual searches on Google Scholar. During the initial screening, 12 duplicate and irrelevant articles were excluded based on their titles. Subsequently, a further 45 irrelevant studies were removed after reviewing their abstracts. Finally, the full-text articles were assessed, leading to the exclusion of an additional 15 studies due to their lack of relevance or unsuitable data.

The remaining nine articles underwent a qualitative evaluation using the STROBE guidelines for cross-sectional studies. Those articles that scored above 80% were considered to meet the quality criteria and were included in the meta-analysis. The steps of article inclusion in this systematic review and meta-analysis are illustrated in Figure 1. It is important to note that the results of the quality evaluation for these articles are provided in the appendix.

Data extraction

For the completion of the meta-analysis, a data extraction

form was developed. This form included various items such as author(s), year of publication, country, study duration, sample size, statistical population, patient characteristics, gender distribution, type of healthcare services received, type of insurance, total costs, and patients' out-of-pocket (OOP) share. The necessary data were then extracted from all included articles, and the results are presented in Table 2.


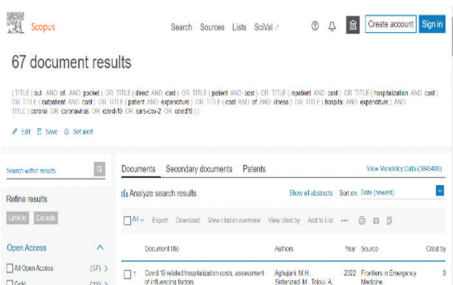
As shown in Table 2, the majority of articles (44%) were published in 2021, with a significant focus on studies conducted in the United States (44%). Furthermore, the largest percentage of studies (44%) involved sample sizes exceeding 1000 patients.

Statistical analysis

All statistical analyses for this study were conducted using Stata 16, employing a suite of commands specifically designed for meta-analysis. The degree of homogeneity and heterogeneity was assessed using the I² index. In this study, the I² index values were categorized as follows: values between zero and 25% indicated very low heterogeneity, values between 25% and 50% indicated low heterogeneity, values between 50% and 75% indicated moderate heterogeneity, and values above 75% indicated high heterogeneity.^[13]

Based on the I² index and Cochran's alpha coefficient ($Q = 5.5$ and $P = 0.70$), it was determined that the included articles did not exhibit high heterogeneity, allowing the acceptance of the hypothesis of homogeneity of the means.

Table 1: Results of the systematic search of articles in the databases of PubMed and Scopus

Number of articles	Databases	Search strategies	Results
11	PubMed	((((((((out-of-pocket[Title]) OR (direct cost[Title]) OR (patient cost[Title]) OR (inpatient cost[Title]) OR (hospitalization cost[Title]) OR (outpatient cost[Title]) OR (patient expenditure[Title]) OR (cost of illness[Title]) OR (hospital expenditure[Title]) OR (cost of illness[Title]) OR (patient expenditure[Title]) OR (outpatient cost[Title]) AND (corona OR covid-19 OR SARS-CoV-2 OR covid19 OR coronavirus[Title]))	
67	Scopus	TITLE (Out-AND of-AND Pocket) OR TITLE (direct AND cost) OR TITLE (patient AND cost) OR TITLE (inpatient AND cost) OR TITLE (hospitalization AND cost) OR TITLE (Outpatient AND cost) OR TITLE (patient AND expenditure) OR TITLE (cost AND of AND illness) OR TITLE (hospital AND expenditure) AND (Corona OR Coronavirus OR Covid-19 OR Sars-cov-2 OR Covid19))	

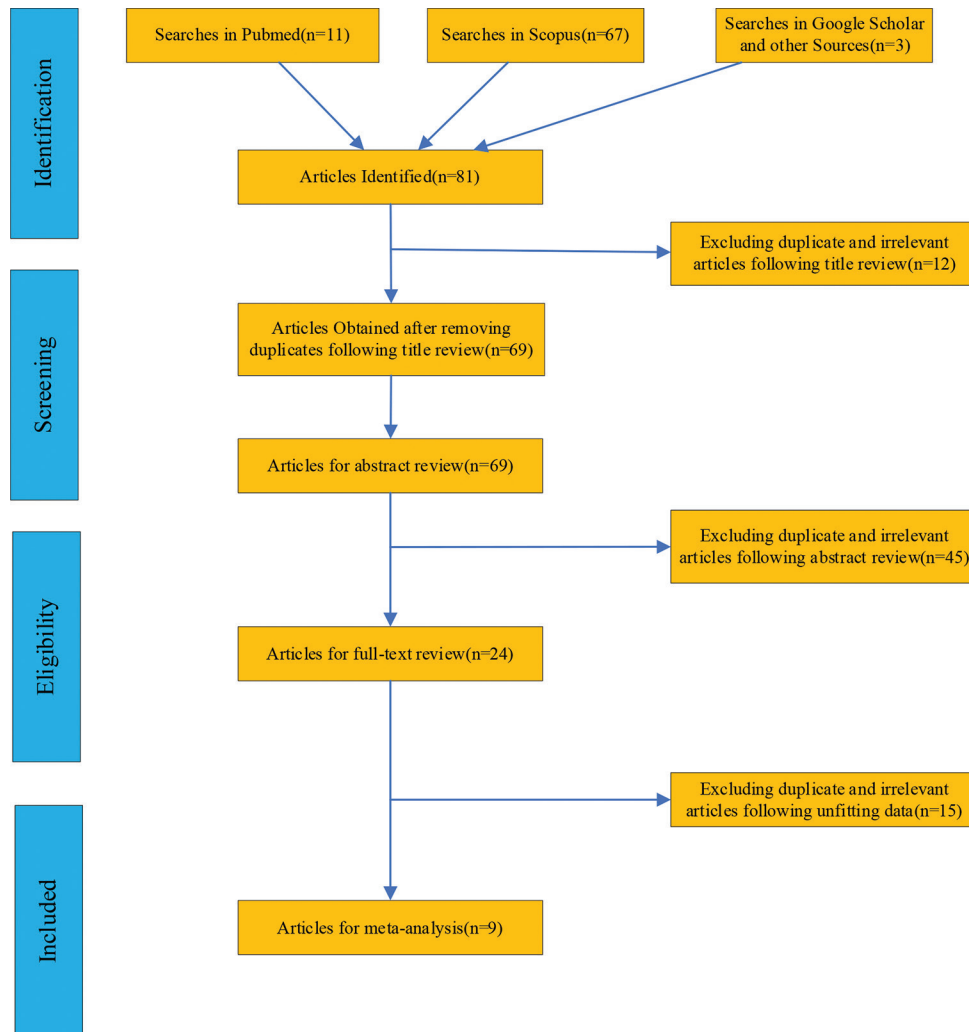


Figure 1: Steps of article inclusion in the systematic review and meta-analysis

Table 2: Features of the articles reviewed

Features	Number of articles (percentage)
Year of publication	
2021	4 (44.44)
2022	5 (55.55)
Year of cost estimation	
2020	6 (66.66)
2021	1 (11.11)
2020-2021	2 (22.22)
Country	
Iran	2 (22.22)
The United States	4 (44.44)
India	2 (22.22)
The Philippines	1 (11.11)
Sample size	
0-500	2 (22.22)
501-1000	3 (33.33)
1000<	4 (44.44)

Therefore, the fixed-effects model (FEM) was employed to estimate the total effect.

To examine the possibility of publication bias, a funnel plot was utilized. Additionally, a sensitivity analysis was conducted using the nonparametric trim-and-fill method developed by Duval and Tweedie (2000).

Ethical considerations

This study was conducted as part of a research project that obtained approval from the National Committee of Ethics in Biological Research in Iran at Baqiyatallah University of Medical Sciences, Tehran, Iran. The project was assigned the code IR.BMSU.BAQ.REC.1400.084.

Results

The results of the meta-analysis for out-of-pocket (OOP) expenditures among patients hospitalized with COVID-19 are presented in Tables 3 and 4. The average OOP expenditures in these patients were US \$308.25, with a 95% confidence interval [CI] ranging from \$4.17 to \$620.67. Among the included studies, the highest reported OOP expenditures were found in the study by

CHAU (2022)^[14] with an amount of US \$3171.28, followed by GRAG (2022)^[15] ranking second with US \$1582.38. The lowest OOP expenditures were reported in the study by KOTWANI (2021)^[16] with an amount of US \$56.35.

Furthermore, in terms of study weight in this meta-analysis, the study by KOTWANI (2021)^[16] had the highest weight, accounting for 35.8%, followed by the study by YUSEFI (2022)^[17] ranking second with a weight of 34.5%. Conversely, the article by CHAU (2022)^[14] had the lowest weight, representing only 0.40%.

Figure 2 demonstrates the presence of publication bias through a funnel plot. However, due to the absence of asymmetry in the articles depicted in this graph, it was not possible to access the results of certain studies or incorporate their data into the meta-analysis. This could be attributed to these studies being published as oral presentations, not being in press yet due to unforeseen results, or undergoing the review process, among other reasons. To address this limitation, the nonparametric trim-and-fill method developed by Duval and Tweedie (2000) was employed. This method allowed for an

estimation of the results of the missing studies, as shown in Figure 3. Consequently, a total of five articles were identified as missing studies, and the meta-analysis results were adjusted accordingly by considering these studies, as presented in Table 5.

Additionally, the meta-analysis results incorporating the missing articles are provided in Table 5. These results indicate that the average OOP expenditures decreased from US \$308,251 to US \$132,403 when accounting for the missing studies.











Discussion

All countries worldwide have been severely impacted by the COVID-19 pandemic, facing numerous challenges such as high mortality rates and economic instability. Hospitalization has been necessary for many individuals diagnosed with COVID-19 globally. Concerns have arisen regarding the financial vulnerability of households in developing nations due to the substantial costs associated with COVID-19 hospitalization, particularly given the heavy reliance on out-of-pocket (OOP)

Table 3: Results of the meta-analysis of OOP expenditures among patients hospitalized with COVID-19

Study	Number of Studies: 9	Heterogeneity: I^2 : 0.00		H^2 : 0.69
	Effect Size	[95% Conf . Interval]		% Weight
Tabunar 2021	733.830	16.275	1451.385	18.96
Kotwani 2021	56.350	-465.838	578.539	35.80
Chua 2022	930.678	-2127.066	3988.422	1.04
Chua 2021	538.089	-1647.011	2723.190	2.04
Chua 2021	519.131	-1708.035	2746.297	1.97
Garg 2022	1582.382	-484.559	3649.323	2.28
Chua 2022	3171.287	-1783.956	8126.531	0.40
Yusef 2022	167.690	-363.872	699.252	34.54
Nakhaei 2021	382.790	-1431.627	2197.207	2.96
Theta	308.251	-4.171		620.673
Test of theta=0: $Z=1.93$		prob> z =0.0531		
Test of homogeneity: $Q=Chi2(8)=5.50$		prob>Q=0.7032		

Table 4: Forest plot of the meta-analysis results of OOP expenditures among patients hospitalized with COVID-19

Study	Effect Size	Effect Size With 95% CI	% Weight
Tabunar 2021		733.830 [16.275, 1451.385]	18.96
Kotwani 2021		56.350 [-465.838, 578.539]	35.80
Chua 2022		930.678 [-2127.066, 3988.422]	1.04
Chua 2021		538.089 [-1647.011, 2723.190]	2.04
Chua 2021		519.131 [-1708.035, 2746.297]	1.97
Garg 2022		1582.382 [-484.559, 3649.323]	2.28
Chua 2022		3171.287 [-1783.956, 8126.531]	0.40
Yusef 2022		167.690 [-363.872, 699.252]	34.54
Nakhaei 2021		382.790 [-1431.627, 2197.207]	2.96
Overall		308.251 [-4.171, 620.673]	

Heterogeneity: I^2 : 0.00 H^2 : 0.69
 Test of $\Theta_i = \Theta_j$: $Q(8) = 5.50$, $P=0.70$
 Test of $\Theta=0$: $Z=1.93$, $P=0.05$

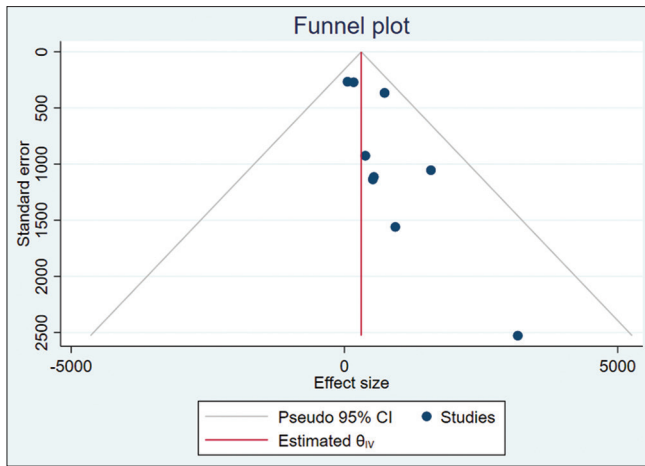


Figure 2: Funnel plot

Table 5: Meta-analysis results of OOP expenditures among patients hospitalized with COVID-19 in terms of publication bias

Number of studies=14	Observed=9	Imputed=5	
Studies	Effect Size	[95% Conf. Interval]	
Observed	308.251	-4.171	620.673
Observed + Imputed	132.403	-147.341	412.147

expenditures within national health systems.^[15] These high costs have been linked to adverse effects, including limited access to healthcare services, especially among the most economically disadvantaged populations. Apart from the physical and psychological hardships brought about by the pandemic, households in various countries have also faced significant financial burdens. COVID-19 has further exacerbated the financial strain on patients, leading to income loss and reduced financial resources.^[7] Consequently, the measurement and monitoring of healthcare costs are crucial for policymakers in developing appropriate strategies to protect patients. The OOP expenditures borne by households and the subsequent catastrophic health expenditures (CHEs) are therefore key factors that must be considered in healthcare planning and policymaking.^[17]

In light of these considerations, insurers and physicians can explore three steps to mitigate the financial burden on patients regarding professional and ancillary services associated with COVID-19 hospitalization. Firstly, limited-scope insurers may consider implementing a blanket waiver, which would encompass all services provided from admission to discharge. This approach aims to alleviate the financial responsibilities of patients in relation to these services. Secondly, it is essential for insurers to ensure the effective implementation of such waivers, providing clear guidelines and mechanisms for coverage. Lastly, physicians can play a role by encouraging patients to contest bills for professional

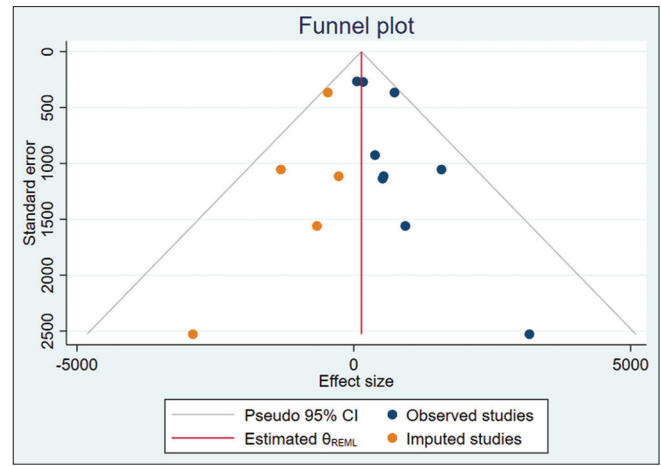


Figure 3: Funnel plot of identified articles and estimation of missing studies

and ancillary services that are covered by cost-sharing exemptions issued by these insurers.^[18]

During the COVID-19 pandemic, there has been a significant increase in out-of-pocket (OOP) expenditures for healthcare services in both the private and public sectors. This surge in expenses has pushed many households toward poverty, exacerbating their already vulnerable situation. Interestingly, this rise in OOP expenditures has occurred despite the presence of health insurance, highlighting the increased risk of poverty among patients. Particularly in low-income countries, where insurance coverage and social support may be lacking, the impact of OOP expenditures on households has been even more pronounced, compounding the problems faced by these individuals.^[17]

One study conducted in Iran estimated the direct and indirect major medical expenses (MMEs) for the treatment of COVID-19, revealing a substantial economic burden of US \$1,439,083,784 on hospitalized patients.^[19] Similarly, Jin *et al.* (2021) conducted a survey in China to assess the financial burden of COVID-19 and reported total health and social costs of US \$0.62 billion and US \$383.02 million, respectively.^[20] In the United States, Chen *et al.* (2021) conducted a study estimating the 10-year (2020-2030) economic burden of COVID-19, which amounted to US \$1.4 trillion, equivalent to 7.7% of the gross domestic product (GDP) in 2019 (at constant US \$2010).^[21] These findings highlight the significant burdens that COVID-19 has placed on both individual patients and populations at large.

According to a survey conducted in Peru, the OOP expenditures for COVID-19 hospitalization were found to be high, and health insurance was ineffective in mitigating these costs.^[22] Studies conducted in the United States also reported substantial OOP expenditures for COVID-19 hospitalization among

insured individuals.^[18,23] Instances of price gouging by private hospitals for COVID-19 healthcare services were identified in several African countries. Within most health systems, service providers tend to hold more power than patients,^[24,25] and this power asymmetry appeared to have worsened during the pandemic, especially during times of panic. Some have advocated for governments to procure healthcare services for COVID-19 from private hospitals. However, Garg (2022) concluded that having public or private health insurance did not effectively reduce OOP expenditures. Moreover, multivariate analyses have shown that private hospitals were the primary contributors to catastrophic health expenditures (CHEs), with hospitalization in such facilities incurring higher costs compared to public hospitals.^[15] Yusefi *et al.* (2022) conducted a study in Iran and found that 57.12% of OOP expenditures for hospitalized patients were associated with pharmaceutical services, which accounted for the largest share. Additionally, a significant relationship was observed between OOP expenditures paid by hospitalized patients and the length of stay.^[17]

Notably, the spread of the COVID-19 disease has had adverse effects on household economies and has made them vulnerable to healthcare costs, especially those incurred by patients during the course of treatment. Given that COVID-19 is an emerging disease, there are limited empirical data and studies available on its costs and OOP expenditures among patients. Moreover, the few studies on the OOP expenditures among COVID-19 patients have reported varying results. In this study, we conducted a systematic review and meta-analysis to investigate this issue. We reviewed the titles of published articles in this area and analyzed the abstracts of several studies based on a checklist. After the final evaluation, nine articles were included in the meta-analysis. The fixed-effects model (FEM) was used throughout the study due to the homogeneity of the results. The results showed that the average OOP expenditures borne by COVID-19 patients were US \$308.25. The study by Chua *et al.* (2022)^[14] had the largest effect size (3171.29) among the articles, followed by Garg *et al.* (2022)^[15] with an effect size of 1582.38, Chua *et al.* (2022)^[26] with an effect size of 930.68 ranked second and third, respectively, and studies by Tabuñar *et al.* (2021)^[27] with an effect size of 733.83, Chua *et al.* (2021)^[28] with an effect size of 538.09, Chua *et al.* (2021)^[18] with an effect size of 519.13, Nakhaei (2021)^[29] with an effect size of 382.79, Yusefi *et al.* (2022)^[17] with an effect size of 167.69, and Kotwani (2021)^[29] with effect sizes of 56.35, respectively, in terms of average OOP expenditures. Therefore, the OOP expenditure among COVID-19 patients varied across different countries, possibly due to differences in policies regarding the coverage of treatment costs for these patients.

So far, various approaches have been implemented to address the COVID-19 pandemic and its associated OOP expenditures. In India, despite OOP costs accounting for approximately 60% of the total healthcare expenditures in the health system, the central and state governments have made efforts to enhance the capacity of public hospitals and provide free or low-cost services for COVID-19 treatment to the extent possible.^[14] In order to minimize OOP expenditures in the private sector, the Government of Gujarat in India signed a memorandum of understanding with 31 trusted private hospitals across 26 districts, designating them as COVID-19 centers to deliver healthcare services without charge to infected patients. The costs incurred by these centers were subsequently reimbursed by the Government of Gujarat.^[16] In the United States, to alleviate financial burdens on patients, 81 private insurance organizations and the Medicaid Advantage program voluntarily waived a portion or all of the hospitalization costs during 2020. However, these exemptions were only provided to certain patients and did not cover all services.^[18]

In the Philippines, the National Health Insurance Act was established in 1995 to address the need for OOP expenditures, and the National Health Insurance Program has made significant progress toward achieving universal coverage, with a coverage rate of approximately 95%. This program serves as a crucial source of financing for healthcare costs. In 2007, 54% of the country's MMEs were attributed to OOP expenditures. In response to the pandemic, the National Health Insurance Program in the Philippines announced that it would cover all costs for COVID-19 patients. However, as of April 15, 2020, it was announced that patients would be covered under specific treatment packages based on the severity of the disease. Additionally, the general hospital affiliated with the University of the Philippines was designated as a referral center for COVID-19 by the Department of Health on March 20, 2020.^[27]

In this study, the authors made the first attempt to extract and present OOP expenditures incurred by patients hospitalized with COVID-19 through a systematic review and meta-analysis. However, like other studies, there were some limitations to consider. One limitation was that most articles did not provide information on the percentage of expenses paid by patients or the total costs, which resulted in the unavailability of data for measures of dispersion, such as standard deviations. Additionally, instead of using percentages, the analysis focused on average OOP expenditures. Moreover, for articles that presented results for two patient groups separately, a weighted average was calculated and utilized.

Conclusion

In conclusion, despite the implementation of various

policies to reduce out-of-pocket (OOP) expenditures incurred by COVID-19 patients in different countries, our study reveals that the average amount of these costs for hospitalized patients remains significant. Furthermore, there is a notable inequality observed in terms of the OOP expenditure across numerous countries. Therefore, it is crucial to provide consistent policy recommendations in international forums to mitigate such financial burdens for patients in both developed and developing nations, especially in preparation for future pandemics.

To address these challenges, it is imperative to focus on key areas such as the development of robust public health infrastructure, the expansion of insurance coverage to encompass a broader range of healthcare services, and the provision of support packages during pandemics. These measures can help alleviate the financial strain that COVID-19 imposes on households and contribute to more equitable access to healthcare services.

Also, financing policies based on advance payment mechanism and public resources with higher risk accumulation and more optimal risk sharing as a key strategy in achieving universal health coverage reduce financial barriers to access to health care and reduce direct out-of-pocket, payments and finally, the quality of health care is improved. Also, policies such as the establishment of a fund for special and difficult-to-treat patients, increasing the coverage of public insurance and adopting supportive policies in deprived and less privileged neighborhoods and regions, and intensifying the monitoring mechanisms in the plan of public insurance coverage can reduce the effects of out-of-pocket payments on the vulnerable and vulnerable, and reduce the cost of society so that they do not suffer from back-breaking expenses and poverty due to such pandemics. Taking preventative measures can also prevent many OOP payments in the future.

The providers' behaviors and actions are also effective in reducing OOP payments. Physicians can replace generic drugs with brand drugs in their prescriptions. Limiting diagnostic-therapeutic tests and surgeries and preventing unnecessary admissions in special intensive care wards and alternative interventions, discharge patients quickly and improve the quality and effectiveness of services, play an effective role in reducing OOP payments.

Given the limited number of articles published in this specific field, it is evident that further research is needed in different countries to better understand and analyze the impact of the COVID-19 pandemic on household healthcare costs and OOP expenditures and its effective factors. This will facilitate the identification of additional strategies to effectively mitigate the financial effects of

future pandemics and promote equitable healthcare access for all, and in order to reduce out-of-pocket payments in such pandemics, appropriate policies should be considered.

List of abbreviations

OOP: out-of-pocket

CHES: catastrophic health expenditures.

Acknowledgment

This article is the result of a service alternative research project entitled (investigating the level of inequality in out-of-pocket payments for COVID-19 patients and related factors in the armed forces health system), which was implemented in the Health Management Research Center of Baqiyatallah University of Medical Sciences. We hereby express our gratitude to all those who helped the researchers in the various stages of this research.

Ethical considerations

This research was derived from an approved research project that was approved by the National Committee of Ethics in Biological Research of Iran with the code IR.BMSU.BAQ.REC.1400.084.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix: Quality evaluation of articles using STROBE guidelines

Section an topic	Item	Checklist item number	Checklist item	(Ali Reza Yusefi <i>et al.</i> , 2022)	(Nakhaei <i>et al.</i> , 2021)	(Samir Garg <i>et al.</i> , 2022)	(Tabuñar <i>et al.</i> , 2021)	(Chua <i>et al.</i> , 2022)	(Chua <i>et al.</i> , 2022)	(Kotwani <i>et al.</i> , 2021)	(Chua <i>et al.</i> , 2022)	Quality evaluation of articles using STROBE guidelines
Title and abstract	Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	✓	✓	✓	✓	✓	✓	✓	✓	✓
			(b) Provide in the abstract an informative and balanced summary of what was done and what was found	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Introduction Background/rationale Objectives	2	Explain the scientific background and rationale for the investigation being reported	✓	✓	✓	✓	✓	✓	✓	✓	✓
		3	State specific objectives, including any prespecified hypotheses	✓	✓	✓	✓	✓	✓	✓	✓	✓
Methods	Study design	4	Present key elements of study design early in the paper	✓	✓	✓	✓	✓	✓	✓	✓	✓
		5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓	✓	✓	✓	✓	✓	✓	✓	✓
Results	Bias	9	Describe any efforts to address potential sources of bias	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Study size	10	Explain how the study size was arrived at	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	✓	✓	✓	✓	✓	✓	✓	✓	✓
			(b) Describe any methods used to examine subgroups and interactions	*	*	*	*	*	*	*	*	*
	Results Participants		(c) Explain how missing data were addressed	x	x	x	x	x	x	x	x	✓
			(d) If applicable, describe analytical methods taking account of sampling strategy	*	*	*	*	*	*	*	*	*
			(e) Describe any sensitivity analyses	✓	✓	✓	✓	✓	✓	✓	✓	✓
		13	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	x	x	✓	x	x	x	x	x	✓
			(b) Give reasons for non-participation at each stage	x	x	✓	x	x	x	x	x	✓
			(c) Consider use of a flow diagram	x	x	✓	x	x	x	x	x	x

Contd...

Appendix: Contd...

Section and topic	Item	Checklist item number	Checklist item	(Ali Reza Yusefi et al., 2022)	(Ali Nakhaei et al., 2021)	(Samir Garg et al., 2022)	(Tabuñar et al., 2021)	(Chua et al., 2022)	(Chua et al., 2022)	(Kotwani et al., 2021)	(Chua et al., 2022)	Quality evaluation of articles using STROBE guidelines		
Descriptive data		14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	✓	✓	✓	✓	✓	✓	✓	✓	✓		
			(b) Indicate number of participants with missing data for each variable of interest	x	x	x	x	x	x	x	x			
			Report numbers of outcome events or summary measures	✓	✓	✓	✓	✓	✓	✓	✓			
			16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓	✓	✓	✓	✓	✓	✓	✓		
Outcome data	Main results		(b) Report category boundaries when continuous variables were categorized	✓	✓	✓	✓	✓	✓	✓	✓	✓		
			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	*	*	*	*	*	*	*	*	*		
			17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	✓	✓	✓	✓	✓	✓	✓	✓	✓	
			Discussion	key results	18	Summarize key results with reference to study objectives	✓	✓	✓	✓	✓	✓	✓	✓
19	Summarize key results with reference to study objectives	✓			✓	✓	✓	✓	✓	✓	✓			
Limitations			Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓	✓	✓	✓	✓	✓	✓	✓	✓		
			20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓	✓	✓	✓	✓	✓	✓	✓	✓	
			Generalizability	21	Discuss the generalizability (external validity) of the study results	✓	✓	✓	✓	✓	✓	✓	✓	✓
				22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓	✓	✓	✓	✓	✓	✓	✓	✓
Other information				82%	82%	93%	82%	82%	82%	82%	82%	93%		