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A meta-analysis of long-term COVID-19 symptoms

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ABSTRACT

This meta–analysis examines the far–reaching effects of long COVID (LC), highlighting the need for welfare strategies emphasizing the Parity of Esteem. The analysis of clinical studies reveals the prevalence of LC across various demographic factors, including age, gender, infection type, and severity. The findings highlight persistent pulmonary impairments that result in post-COVID pulmonary fibrosis (PCPF), long-term cardiovascular symptoms, gastrointestinal issues, dermatological concerns, and neuropsychiatric outcomes. These effects continue beyond the acute phase of COVID-19, affecting both symptomatic and asymptomatic people. The study emphasizes that LC is not only a physical ailment but also has a significant impact on mental health, necessitating a holistic approach to healthcare. Psychological and emotional distress among LC patients necessitates empathetic support. This study concludes by emphasizing the significance of LC and advocating for data-driven healthcare policies and assistance programs to address the unique challenges encountered by COVID-19 survivors. For managing the long-term effects of LC on both physical and mental health, an unwavering commitment to parity of esteem is crucial.

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1. INTRODUCTION

Long COVID-19 (LC) has emerged as a significant global health concern, necessitating attention to the diminishing awareness of post-COVID-19 effects [1]. LC affects not only COVID-19 survivors but also their immediate social circles, including their families, acquaintances, coworkers, and communities. This persistent condition affects individuals of all ages and genders, infection types (symptomatic or asymptomatic), and severity levels (mild, moderate, severe, and critical). In addition, specific demographic factors have been associated with the prevalence of distinct LC symptoms [2]–[3].

Recent clinical studies have played a crucial role in evaluating LC symptoms, shedding light on its diverse impacts on different organ systems [4]. Pulmonary impairments attributable to viral pneumonia and severe acute COVID-19 are prevalent in patients with LC [5]. In addition, COVID-19 survivors continue to experience cardiovascular impairments, including fatigue, dyspnea, and chest symptoms [6]. Notably, post-

acute COVID-19 infection of the gastrointestinal tract is characterized by dysbiosis and chronic inflammation [7]. Long-term neuropsychological effects can range from mild to severe, and diminished attention, memory problems, and learning impairments may persist [8]. Moreover, the mortality brought about by the pandemic increased hostility and psychological distress among bereaved family members and companions of COVID-19-infected individuals, disrupting cultural worldviews, self-esteem, and personal relationships, thereby affecting the social fiber of the community [9].

Parity of Esteem is a fundamental principle that advocates for physical and mental health aspects of LC to receive equal attention and importance [10]. In the context of the COVID-19 pandemic, the significance of this concept increases even further. As initial attention shifted towards diagnosing, treating, and preventing the virus, the long-term effects of COVID-19, known collectively as LC, were somewhat overshadowed. Recognizing that LC is not only a physical disorder but also one that significantly affects the mental and emotional health of individuals, Parity of Esteem acknowledges the need to address both aspects of LC equally. Individuals with a chronic condition such as LC require a comprehensive approach to healthcare that addresses all aspects of their health.

To emphasize the importance of LC, it is crucial to provide empirical evidence, mainly through meta-analysis. This empirical data will provide a comprehensive overview of LC's impact and prevalence, providing compelling evidence for refocusing attention on this persistent health concern. Through the presentation of robust empirical data, specific demographic factors such as gender, smoking habits, and comorbidities can be identified so that the Philippine healthcare community can advocate for Parity of Esteem, ensuring that policymakers will be able to formulate and implement strategies and interventions that can lead to more effective management and improved quality of Life for those battling LC.

2. METHOD

The meta-analysis of general, musculoskeletal, neurological, psychological, respiratory, cardiovascular, ear, nose, and throat (ENT), gastrointestinal, and dermatological LC symptoms was done following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), 2009 [11]. The R software application was utilized [12].

2.1. Study selection and eligibility criteria

The prevalence of long-term COVID-19 symptoms between January 1, 2021 and April 30, 2023 was researched using open–access databases such as PubMed, Science Direct, and Google Scholar, utilizing a Boolean search comprised of keywords associated with the various categories of LC symptoms. The titles and abstracts of selected studies were subjected to preliminary screening. The following criteria determined the eligibility of studies: i) Study design: cohort and cross-sectional studies ii) The subjects are self–reported and polymerase chain reaction (PCR)-verified COVID-19 survivors iii) Sample size: 30>patients, iv) Follow-up time: >4 weeks, v) Demographic information, and vi) Test parameters including survey questionnaires, medical records, and diagnostic tests.

2.2. Data extraction and analysis

The following characteristics of the study were extracted: author, country, study design, sample size, longest follow-up period, gender, age, COVID-19 diagnosis, comorbidities, hospitalization status, and number of smokers. The estimated combined prevalence of LC symptoms with a frequency of >5 was determined by utilizing the "Inverse" procedure in R [13]. The outcomes were presented as proportion estimates, I2 and Q statistics, and heterogeneity p-values (if significant: 0.05).

Subgroup analyses for demographic risk factors were independently conducted in R software using a random effects model based on the univariate regression outcome of studies reporting age, gender, smoking status, presence of comorbidities, presence of comorbidities (hypertension and diabetes), and intensive care unit (ICU) admission. Forest plots were used to illustrate the results. Prospective publication bias was visualized using a funnel plot, and the likelihood of publication bias was quantitatively assessed using a linear regression test.

2.3. Quality assessment of included studies

The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS), consisting of eight items distributed across three domains: selection, comparability, and outcome. The following metrics were used to assign stars to each domain to determine the study's quality:

- Good quality: 3 or 4 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain.

- Fair quality: 2 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain.
- Poor quality: 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 star in the outcome/exposure domain.

3. RESULTS AND DISCUSSION

The heightened interest in elucidating the causes, effects, and management of long-term COVID-19 (LC) is reflected in the large number of studies uncovered by exhaustive literature searches, as depicted by the PRISMA diagram as shown in Figure 1.

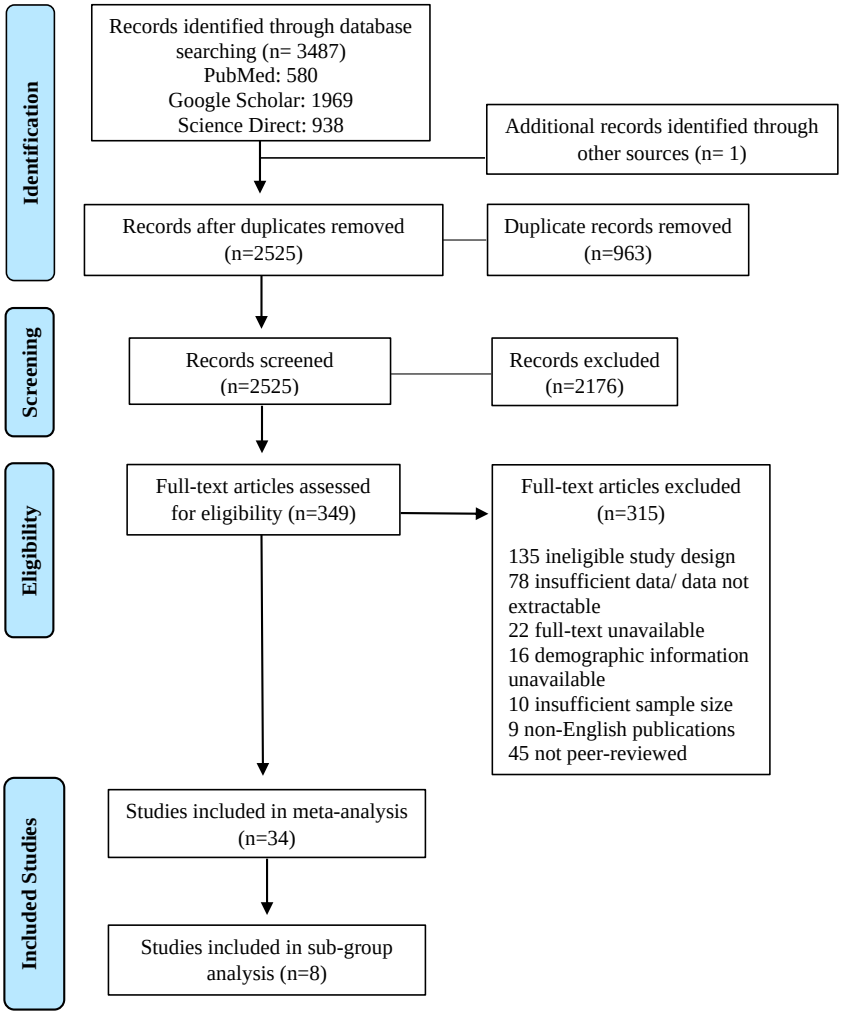

Figure 1. PRISMA flow diagram

3.1. Study characteristics

Table 1 displays the characteristics of the 34 included publications [14]–[47], which report a total population of 21,679 and an estimated median (sample size range) of 302.5 (46–3065). The mean (SD) age is estimated to be 51.76 years (4.94). Approximately the same proportion of males (49%) and females (48%) comprise the total population, and 58% of the population was hospitalized for acute COVID-19 infection. The most frequently reported comorbidities are hypertension, diabetes, cardiac issues, chronic obstructive pulmonary disorder (COPD), and chronic kidney disease (CKD), and most studies had follow-up periods of 6 to 12 months. The majority of publications originated from China, the United States, the United Kingdom, Spain, and France, and the majority (31/34) were cohort studies.

3.2. Study quality

There were 14 publications with research of high quality, 18 with moderate quality, and 2 with poor quality analysis. Inadequate sample size or underrepresentation of study population, absence of control groups, uncertainty of outcomes with respect to pre-long COVID phase, unrecorded potential risk factors, lack of methods to account for confounding variables, subjective assessment of symptoms or lack of objective functional measures, insufficient follow-up time, and issues with data collection and patient follow-up were the main reasons for non-awarding of stars.

Table 1. Characteristics of included studies

Characteristics	n (%)
Total study population	21,679
sample size, mean (range)	302.5 (46-3065)
Age, mean (SD)	51.76 years (4.94)
Gender, *n* (%)	
Male	10,570 (48)
Female	10,335 (49)
Unstated	774 (6)
Hospitalization, *n* (%)	
Hospitalized	12, 523 (58)
Non – hospitalized	7,524 (35)
Comorbidities, no. of studies	
Hypertension	27
Diabetes	25
Cardiac problems	18
Chronic obstructive pulmonary disorder (COPD)	17
Chronic kidney disease (CKD)	16
Cancer, Asthma	13
Asthma	13
Obesity, cardiovascular disease (CVD)	7
Immunosuppression, chronic liver disease (CLD), cerebrovascular disease	6
Stroke, dyslipidemia	4
Respiratory affection, psychiatric disease	1
Follow-up time	
<6 months	8
6-12 months	21
>2 months	2
unstated	3
Study design, no. of studies	
Cohort	31
Cross-sectional	3
Country of origin, no. of studies	
China	6
USA, United Kingdom, Spain, France	3
Brazil, Saudi Arabia	2
Japan, India, Korea, Bangladesh, Iran, Tunisia, Egypt, Italy, Australia, Switzerland, Austria	1

3.3. LC symptoms

3.3.1. Pooled prevalence of LC symptoms

The analysis of quantitative data from 34 included studies, spanning the pandemic years 2021 through the end of the first quarter of 2023, illuminates the long-term health issues that various populations of COVID-19 survivors may experience. Table 2 displays the pooled prevalence results for LC symptoms reported more than five times across all included studies. The range of heterogeneity is between 67.7% and 98.5%, and the vast majority of Q statistics outcomes are highly significant.

The relatively high prevalence of LC symptoms documented in the included studies highlights the substantial impact on the quality of Life of COVID-19 survivors [48], [49]. Notably, fatigue is the most prominent symptom in both acute and chronic COVID-19 infections [50], emerging as the most frequently reported and prevalent LC symptom, often coexisting with a variety of symptoms affecting the respiratory, cardiovascular, neuropsychological, musculoskeletal, and ear, nose and throat (ENT) systems in the majority of studies. Oxidative stress following mitochondrial dysfunction has been identified as a plausible contributor to the LC fatigue mechanism [51], [52]. In the context of respiratory and cardiovascular LC, diagnostic tests such as radiological imaging have acquired prominence in investigating lung and cardiac abnormalities, with approximately one–third of the included studies employing these techniques [53]. Comorbidities identified in

34 publications, including hypertension, diabetes, COPD, pre-existing pulmonary diseases, and obesity, are also consistently cited as prospective risk factors for respiratory and cardiovascular LC [54], [56]. Remarkably, LC manifests diverse neuropsychological and ENT symptoms, as observed in the health effects of COVID-19 on the nervous system [57]. The persistence and invasion of SARS-COV-2 in the central and peripheral nervous systems and persistent inflammation, immune dysfunction, blood coagulation abnormalities, and endothelium dysfunction are among the potential mechanisms underlying these manifestations [58]–[60]. The high prevalence of musculoskeletal, gastrointestinal, and dermatological LC symptoms exemplifies the extensive spectrum of symptom prevalence across multiple organ systems. This may be attributable to multi-organ impairment that persists from the acute phase of COVID-19 infections to the LC phase [58], [61], [62]. The substantial heterogeneity of frequently reported symptoms demonstrates the complexity of LC, particularly in terms of the variations in clinical manifestations across different populations. It also describes the difficulties associated with subjective assessments, such as self-reporting and recall bias, which may have impacted the reporting of LC symptoms in the included studies. According to research, the psychological and social consequences of general, musculoskeletal, cardiorespiratory, gastrointestinal, and dermatological LC symptoms are circumscribed by the physical limitations associated with these symptom categories [63]–[67]. In the pursuit of comprehensive understanding, these findings provide a compelling impetus to integrate the Parity of Esteem further to illuminate the path toward a more balanced and holistic healthcare approach for LC.

Table 2. Pooled prevalence (PP) of LC symptoms from 34 included studies

LC symptom	Proportion estimates, *PP [95% CI)*	I^2 (%)	Q statistic	p-value
General symptoms:				
Fatigue	0.2389 [0.1838; 0.3043]	97.4	1019.94	<0.0001
Fever	0.0173 [0.0108; 0.0275]	67.7	30.99	0.0006
Musculoskeletal symptoms:				
Myalgia	0.0895 [0.0643; 0.1233]	97.1	786.39	<0.0001
Arthralgia	0.1297 [0.0857; 0.1916]	96.8	536.92	<0.0001
Neurological symptoms:				
Headache	0.0782 [0.0540; 0.1119]	96.8	856.97	<0.0001
Dizziness	0.0750 [0.0525; 0.1062]	93.4	256.15	<0.0001
Sleep problems	0.1601 [0.1112; 0.2250]	96.2	497.01	<0.0001
Brain fog	0.1260 [0.0557; 0.2603]	98.2	278.36	<0.0001
Concentration problems	0.1554 [0.0730; 0.3007]	96.8	188.18	<0.0001
Memory problems	0.1110 [0.0618; 0.1915]	97.3	452.16	<0.0001
Peripheral neuropathy	0.0481 [0.0193; 0.1147]	95.9	193.53	<0.0001
Visual disturbances	0.0318 [0.0148; 0.0669]	84.3	44.48	<0.0001
Psychological symptoms:				
Depression	0.1563 [0.0970; 0.2419]	97	234.56	<0.0001
Post-traumatic stress disorder (PTSD)	0.0509 [0.0252; 0.1003]	94.4	106.3	<0.0001
Anxiety	0.1288 [0.0945; 0.1732]	90.4	93.34	<0.0001
Respiratory symptoms:				
Cough	0.0642 [0.0436; 0.0934]	95.2	454.48	<0.0001
Shortness of breath	0.2041 [0.1141; 0.3381]	98.1	467.59	<0.0001
Dyspnea	0.1235 [0.0661; 0.2190]	98.4	1057.51	<0.0001
Expectoration	0.0241 [0.0120; 0.0478]	78.2	27.57	0.0001
Cardiovascular symptoms:				
Chest pain	0.0510 [0.0293; 0.0871]	96	424	<0.0001
Palpitation	0.0730 [0.0446; 0.1174]	93.1	173.18	<0.0001
Ent symptoms:				
Nasal symptoms	0.0521 [0.0309; 0.0865]	92.2	64.11	<0.0001
Smell problems	0.0695 [0.0440; 0.1081]	98.5	1548.96	<0.0001
Taste problems	0.0523 [0.0349; 0.0776]	93.8	321.03	<0.0001
Tinnitus	0.0485 [0.0262; 0.0881]	92.3	78.14	<0.0001
Odynophagia and dysphagia	0.0330 [0.0222; 0.0486]	92.9	196.85	<0.0001
Gastrointestinal symptoms:				
Nausea and vomiting	0.0148 [0.0065; 0.0333]	89.1	55.04	<0.0001
Abdominal pain	0.0268 [0.0104; 0.0672]	92.2	89.87	<0.0001
Diarrhea	0.0195 [0.0136; 0.0280]	71.7	31.75	0.0002
Weight loss & reduced appetite	0.0345 [0.0232; 0.0510]	87.8	106.78	<0.0001
Dermatological symptoms:				
Hair loss	0.1015 [0.0611; 0.1639]	89.1	82.23	<0.0001
Skin rash	0.0261 [0.0133; 0.0509]	80.7	25.95	<0.0001

3.3.2. Sub–group analysis

The disparities in age and gender associated with LC are a critical aspect of the disease as shown in Figure 2. The significant association of age over 50 and the weak but statistically significant association of female gender with the development of LC indicates that these populations appear to be more prone to

developing LC. On the other hand, data for the remaining risk factors were insufficient to establish statistically significant associations with the prevalence of LC symptoms. The interplay between the multi-systemic nature of LC, the associated risk factors, and prolonged duration of LC symptoms (6-12 months) highlights the need for integrative and holistic approaches to mitigate the health effects of LC on the population. This accords with evidence-based recommendations for rehabilitation and emerging pharmacological therapies concerning LC [68], [69]. The evident protective effect of vaccination against the onset of LC symptoms is consistent with prior research [70], [71]. However, additional validation is required for the inclusion of COVID-19 vaccinations in the recommended strategies and policies for LC management.

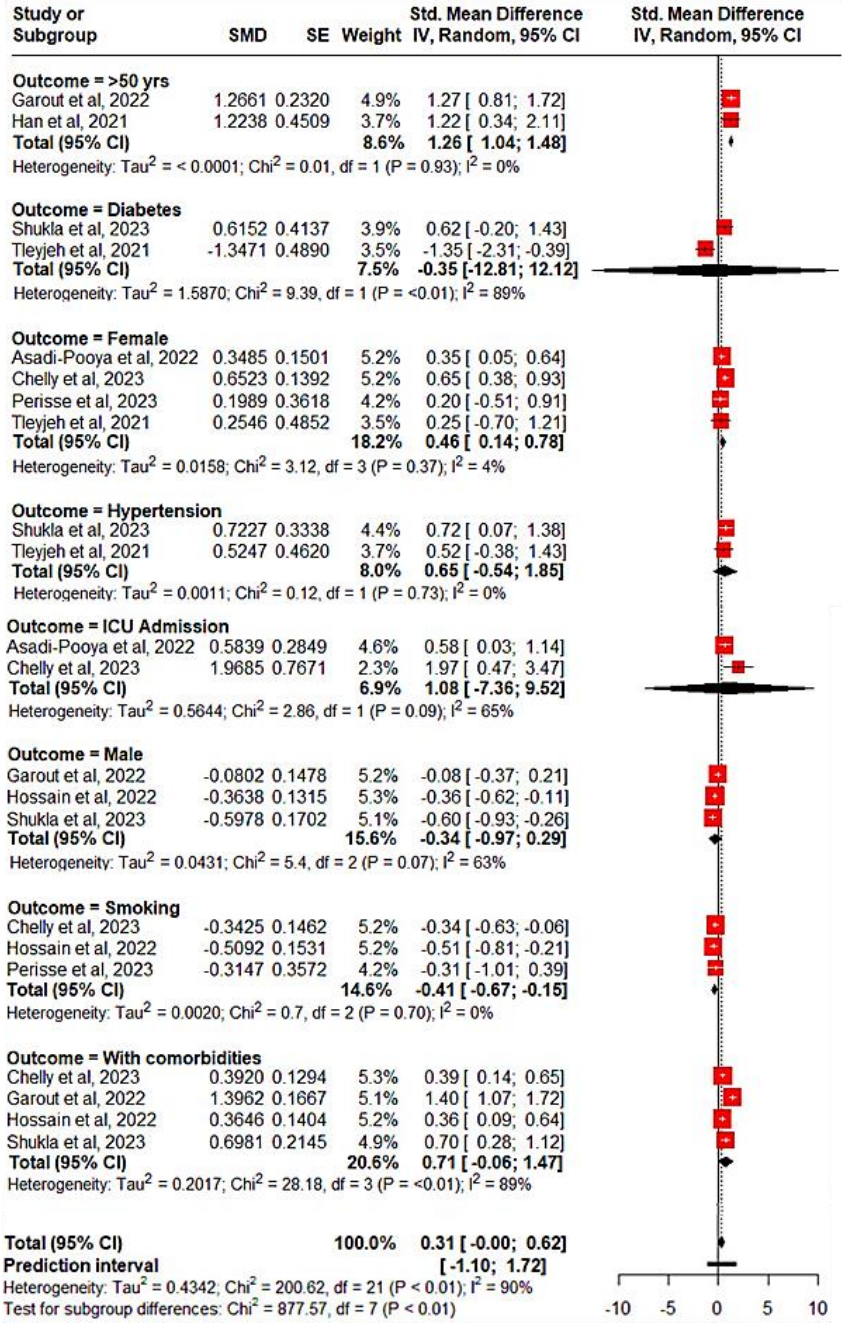

Figure 2. Sub–group analysis for potential LC risk factors: >50 years, gender, smoking status, presence of comorbidities, comorbidities (hypertension and diabetes), and ICU admission

3.3.3. Publication bias

The acknowledgment of publication bias reveals an unequal distribution of studies within the meta-analysis as shown in Figure 3. This disparity may result from a preference for publishing studies with positive or statistically significant results, thereby marginalizing those with less conclusive results and introducing bias [72]. The majority of studies are dispersed in the topmost portion of the plot. As a result, insufficient studies are distributed throughout the graph's lower portion to account for symmetry. Egger's test was performed to quantify the asymmetry in question further.

Table 3 shows that the estimated bias (1,3602) corresponds to the degree of prospective bias depicted in Figure 3. The observed bias is a compelling indicator of research deficiencies in the current landscape. The overrepresentation of studies with specific outcomes for LC, e.g., symptom category, age, gender, and region, may cast a shadow on other necessary research with diverse LC findings [72]. This scenario can result in an incomplete or distorted understanding of LC. The multifaceted nature of this bias may also be attributable to the variations in how the included studies were conducted and their results reported, which added complexity when combining and comparing the studies within the meta–analysis. In contrast, the T statistic is modest (0.87), indicating that the previously mentioned evidence for the bias is meager. The p-value provides further evidence that the asymmetry of the funnel plot is not supported by statistically significant evidence.

The quantitative data exposes a variety of health repercussions, casting light on the significant burden LC places on global healthcare systems and the significance of the Parity of Esteem. This necessitates increased public awareness and the availability of medical facilities equipped to treat LC patients [73], [74]. Nonetheless, it is essential to recognize several limitations that may affect the interpretability and reliability of the study's findings. Due to inconsistencies in defining and reporting LC, it was difficult to directly compare prevalence estimates across studies. Consequently, using the "inverse" method, the estimated aggregated prevalence for each LC symptom was calculated. Additionally, the varying follow-up durations hampered the assessment of the progression of LC symptoms. In addition, the small number of studies included in the subgroup analysis and the underrepresentation of representative populations may influence the generalizations of the study.

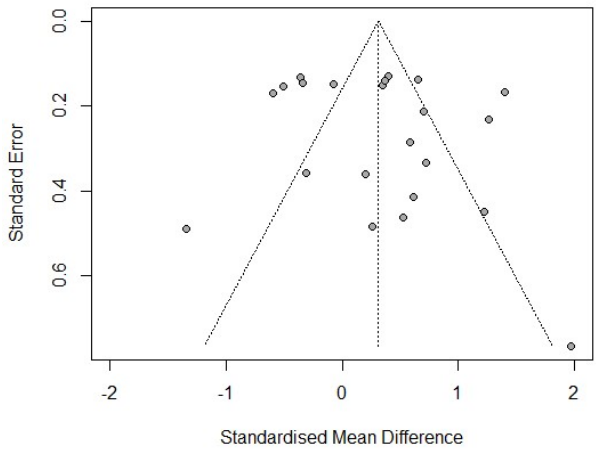

Figure 3. Funnel plot for publication bias showing asymmetry

Table 3. Linear regression test for funnel plot asymmetry

Test result	Value
Estimated bias	1.3602
t-statistic	0.87
p-value	0.3926

4. CONCLUSION

The meta-analysis of available research on long-term COVID demonstrates the complexity of this condition, which is characterized by a wide range of persistent symptoms affecting multiple organs. The statistically significant associations between age and gender and LC risk require additional validation to comprehend the demographic factors. The notable heterogeneity in symptom prevalence estimates highlights the need for objective and subjective evaluations to obtain more accurate and reliable data. LC imposes a

significant burden on those who experience it, highlighting the imperative need for interventions to mitigate its negative health consequences among COVID-19 survivors. In addition, the study emphasizes the significance of recognizing and addressing the mental health effects of LC, which have been largely ignored, particularly in various sectors. This oversight can have a negative effect on the well-being and performance of individuals in society as a whole. In light of these findings, the following LC management practices are recommended for effective healthcare planning and management of LC in the Philippines. i) elevated LC awareness and programs, ii) embracing Parity of Esteem in both government and private sectors, most significantly, academic institutions for a holistic approach to LC management in these organizations, and iii) Further research collaborations focusing on sub–groups, comprehensive examination of co-occurring LC symptoms, and exploration of LC's effects on carers and significant others of COVID-19 survivors.

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