گزارش نهایی طرح تحقیقاتی

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THE FREQUENCY OF CO-INFECTIONS IN PATIENTS WITH COVID-19 IN INTENSIVE CARE UNITS: SYSTEMATIC REVIEW AND META-ANALYSIS

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INTRODUCTION

- عفونت‌های بیمارستانی یکی از عوارض جانبی مراقبت از بیماران است. پیدایش بخش‌های مراقبت ویژه در درمان اساسی ارگان‌ها باعث بهبودی بیماران شده که در غیر اینصورت به مرگ محکوم می‌شوند. این در حالی است که طولانی بودن مدت بستری در این بخش‌ها و استفاده از انواع دستگاه‌های نگه دارنده و مانیتورنیگ تهاجمی و انواع کاتترهای عروقی باعث افزایش خطر ابتلا به عفونت‌های بیمارستان در این بخش‌ها شده است. با وجود اینکه تعداد بیماران بستری در ICU کمتر از سایر بخش‌های بیمارستان است ولی عفونت بیمارستانی در این بیماران حدود ۵-۱۰ برابر میزان عفونت بیمارستان در بیماران موجود در سایر بخش‌های بیمارستان است

INFECTION

- از جمله عوامل تاثیرگذار در افزایش میزان عفونت بیمارستان می‌توان به مشکلات سیستم ایمنی، مصرف داروهای سرکوب‌کننده ایمنی، بیماری‌های مزمن مثل دیابت، سیروز، نارسایی کلیوی و سرطان‌ها و مصرف آنتی‌بیوتیک‌های بسیار اشاره کرد. همچنین بعضی مداخلات درمانی مثل لوله‌گذاری، رگ‌گیری و ... نیز در افزایش شیوع عفونت بیمارستانی نقش بسزایی دارد. استفاده از مداخلات درمانی تهاجمی مثل بازکردن راه هوایی، کارگذاری انواع کاتتر، سن و جسن بیمار، تغییر در تمامیت پوست، خدمات تروماتیک، جراحی‌های متعدد، اختلال در مکانیسم‌های دفاعی در مقابل عفونت‌ها و ابتلا به بیماری‌های زمینه‌ای از جمله عوامل خطرساز برای ایجاد انواع عفونت‌ها در بیمارستان است

COVID-19…

- کرونا ویروس از دسامبر سال ۲۰۱۹ میلادی، از شهر ووهان چین آغاز و هم اکنون تبدیل به یک پاندمی جهانی شده و بیش از ۲۰۰ کشور جهان را درگیر نموده است. علایم این بیماری شامل تب، سرفه، تنگی نفس، ضعف و گلودرد می‌باشد. بسیاری از بیماران مبتلا به کووید ۱۹ بستری در بخش‌های ویژه نیز از عفونت های بیمارستانی مستثنی نمی‌باشند
- A review of 37 published articles with 24983 participants showed that the ICU-admission rate and mortality among ICU admitted patients with covid-19 were 32% and 39%, respectively
- . لذا با توجه به شیوع بیماری کووید ۱۹ و افزایش بیماران بستری در بخش‌های ویژه و اهمیت کنترل عفونت‌های بیمارستانی، در این مطالعه مروری به **بررسی فراوانی عوامل ایجادکننده عفونت‌های همراه در بیماران مبتلا به کووید در بخش‌های مراقبت ویژه پرداخته خواهد شد.**

METHOD

- این مطالعه یک مرور سیستماتیک است که به منظور بررسی فراوانی عوامل ایجادکننده عفونت‌های همراه در بیماران مبتلا به کووید در بخش مراقبت‌های ویژه انجام خواهد شد. مطالعه بر اساس راهنمای نگارش Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) تدوین گردید . با توجه به ماهیت سؤال پژوهش، فرمول‌بندی سؤال بر اساس ساختار PECO به شرح زیر انجام شد:
  - P: بیماران مبتلا به کووید-۱۹
  - E: عوامل ایجادکننده عفونت در بخش مراقبت‌های ویژه
  - C: ---
  - O: عفونت‌های همراه

Synonyms	keyword	
COVID19; 2019-nCoV Infection; 2019 nCoV Infection; Coronavirus Disease-19; Coronavirus Disease 19; SARS Coronavirus 2 Infection; SARS-CoV-2 Infection; SARS CoV 2 Infection; SARS-CoV-2 Infections; COVID-19 Pandemics; COVID 19 Pandemic	COVID-19	جمعیت/ بیماری
ICU; Intensive care unit	Intensive Care Units	مواجهه
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Cross Infections; Healthcare Associated Infections; Health Care Associated Infections; Hospital Infections; Nosocomial Infections; Virus Diseases; Viral Infections; Viral Diseases; Mycoses; Fungus Infections; Fungus Diseases; Bacterial Infections; Bacterial Diseases; Respiratory Tract Infections; Respiratory Infections; Upper Respiratory Tract Infections; Upper Respiratory Infections; co-infections	Cross Infection; coinfection	پیامد

SEARCH STRATEGY AND STUDY SELECTION

- در این مطالعه پایگاه‌های اطلاعاتی PubMed, Web of science (WOS), Scopus, Embase, Science direct, Cochrane جستجو خواهد شد.
- همچنین، به منظور بازیابی منابع خاکستری (Gray literature)، مجموعه مقالات کنفرانس‌ها و همایش‌های مرتبط به صورت دستی جستجو خواهد شد. بعلاوه، پس از مشخص شدن منابع نهایی، فهرست منابع آن‌ها برای یافتن مطالعه‌های مرتبط بیشتر بررسی خواهد شد.

INCLUDING AND EXCLUDING CRITERIA

- در این مرور سیستماتیک تمام مطالعات مشاهده‌ای شامل مطالعات مقطعی (Cross-Sectional)، گزارش موردی (case reports)، گزارش موارد (Case series)، هم گروهی (cohort)، مورد شاهدی (case-control) مرتبط با حوزه عفونت‌های بیمارستانی در بخش مراقبت‌های ویژه در بیماران کووید ۱۹ بین سال‌های ۲۰۱۹ تا ابتدای ۲۰۲۲ا بدون محدودیت زبان وارد شدند.

انتخاب منابع و بررسی اعتبار علمی مقالات و منابع

- نتایج جستجوی منابع وارد نرم‌افزار Mendeley شد. پس از آن در مرحله اول موارد تکراری حذف شد. سپس، عنوان و چکیده منابع باقی مانده بر اساس معیارهای ورود و خروج بررسی و موارد نامرتبط حذف گردید. پس از آن متن کامل منابع باقی مانده بازیابی شد. در خصوص مقالاتی که متن کامل آنها در دسترس نیست با نویسندگان مقاله تماس گرفته شد. چنانچه پس از ارسال ایمیل در فواصل زمانی یک ماهه موفق به اخذ متن کامل نشدیم، اقدام به خرید منبع شد و در صورتی که خرید منبع هم امکان‌پذیر نباشد، آن منبع از مرور حذف شد. در نهایت، منابعی که متن کامل آن‌ها پیدا شد، بر اساس معیارهای ورود و خروج مورد بررسی قرار گرفت و منابع نهایی جهت ورود به مرور انتخاب شد. مراحل غربالگری عنوان/چکیده و متن کامل توسط دو نفر از اعضای تیم پژوهش انجام شد.

- ارزیابی کیفیت منابع نهایی توسط دو نفر از اعضای تیم پژوهش به طور مستقل انجام شد. در صورتی که توافق نظر در موارد اختلاف حاصل نشد از نفر سوم خبره در این زمینه استفاده شد

DATA EXTRACTION

- اطلاعات هر منبع شامل نام نویسنده اول، سال انتشار، کشور مورد مطالعه، طرح مطالعه، نمونه مورد مطالعه و عوامل ایجادکننده عفونت‌های بیمارستانی با استفاده از فرم استخراج داده استخراج شد.

QUALITY ASSESSMENT

- The methodological quality of the included studies was assessed using the National Institutes of Health (NIH). A different version of this checklist was assigned to each study type, consisting of 12 items for case-control studies, 9 for case series, and 14 for observational studies (cohort and cross-sectional). Responses indicated whether the article met the questioned criteria with a yes, no, cannot determine/not reported. The final score was calculated by summing the number of yes answers and reported as good (low risk of bias), fair (insufficient bias to invalidate the results), or poor (high risk of bias). The quality of observational studies was classified as poor for scores of 0-4, fair for scores of 5–10, and good for scores of 11–14 . For case-control studies, the overall score was categorized as poor for scores 0-5, fair for scores 6–7, and good for scores 8-12. The quality of case-series studies was categorized as poor for scores 0-3, fair for scores 4-6, and good for scores 7-9. Two researchers independently assessed the included studies and discussed any discrepancies with the research team.

STATISTICAL ANALYSIS

- After extracting information from the articles, the prevalence and 95% confidence interval (95%CI) was reported as an overall effect size. Heterogeneity among the studies was assessed using the I^2 index and Q statistic, and the random or fixed method was used to combine the results. Subgroup analysis was performed to investigate the prevalence in subgroups based on type of study, sex, and microorganism's type. In addition, the meta-regression method was used to investigate the effect of age on the outcome. Publication bias was assessed using Egger's test. If the publication bias was significant, the 'trim and fill' method was used to modify the results. All statistical analyses were performed using Stata version 17

RESULT

- The initial search identified 160 articles, but four were excluded due to duplicates. After title and abstract screening, 114 articles remained for further evaluation. Two researchers carefully reviewed the full texts of these studies and consulted a third reviewer for any discrepancies. Finally, we included 74 articles in the systematic review and summarized the characteristics of all included studies. For the meta-analysis, 32 articles were excluded because the prevalence of the pathogens was not extractable. Therefore, the meta-analysis was performed on 42 articles.

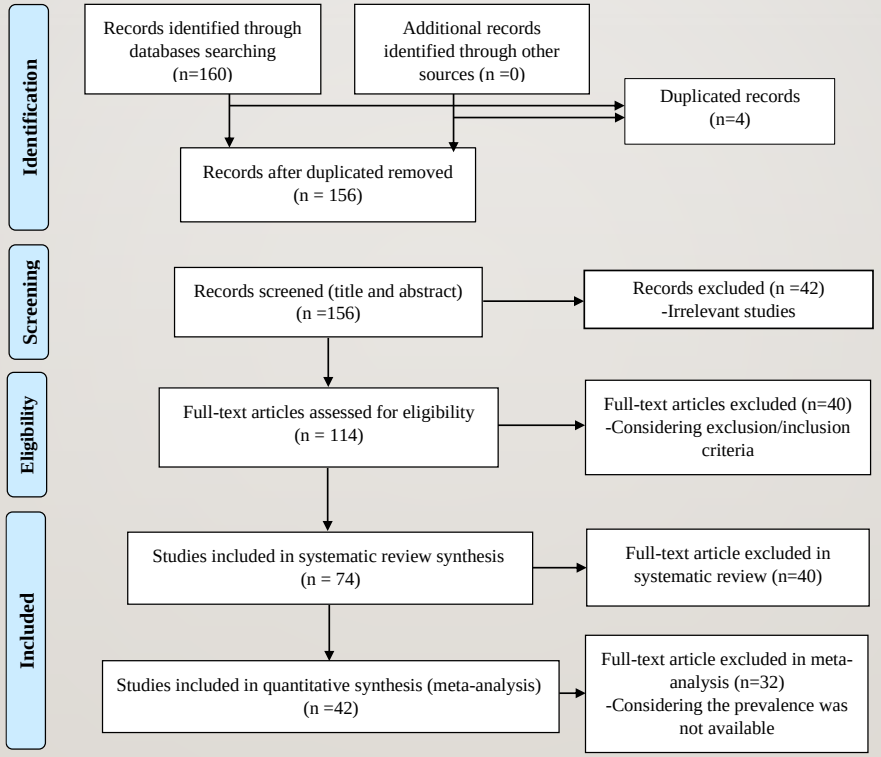

Figure 1. Flow diagram of the inclusion process

- The pooled prevalence of coinfections was estimated at 35% [CI 95%: 29%- 41%], and the results did not change significantly after re-examination according to study type (P= 0.8). The overall prevalence by study types was 37% for case-control studies, 35% for case series, 36% for cohort studies, and 31% for cross-sectional studies
- we could not to obtain comparable results regarding the types of pathogens responsible for coinfection due to methodological differences. Some studies reported the pathogen types based on patient samples taken during hospitalization and did not report them separately for each case. However, among the positive reports of coinfection, 196 cases were bacterial, 37 were fungal, two were viral, and two were contaminated with more than one type of pathogen

- The meta-analysis of 31 studies showed that the incidence of coinfection was significantly associated with gender (P< 0.001), with men having a higher prevalence of 69% compared to women with a prevalence of 31% .
- However, our analysis of the extracted data from 32 articles showed no association between the prevalence of coinfection and age(P=0.65). Although the result of the Egger test was significant (P< 0.001), we performed the trim and fill method to account for any possible modification,

DISCUSSION

- Bacterial coinfections in ICU patients with covid-19
- although bacterial coinfections among covid-19 patients were less common than in previous influenza pandemics, they remained an important challenge in the covid-19 outbreak. Some studies suggested the serum level of procalcitonin as a factor to help clinicians in the differential diagnosis of viral and bacterial infections. A study of 101 ICU patients with confirmed severe covid-19 pneumonia examined respiratory tract samples. They reported 19.8% positive cultures with at least one pathogen. Staphylococcus aureus was the most common pathogen in their patients. In addition, most cases (82.2%) required intubation and mechanical ventilation . A review of 10 published studies in October 2021 stated that bacterial coinfection occurred in less than 4% of hospitalized covid-19 patients and the most common frequencies were related to Staphylococcus aureus, Streptococcus pneumoniae, and Haemophilus influenzae, respectively. This pattern was different in patients with prolonged hospitalization; in these cases, Pseudomonas aeruginosa, Klebsiella spp., and Staphylococcus aureus were more common, respectively.

- A study on hospitalized patients with COVID-19 from a center in Saudi Arabia showed that the rate of positive sputum and blood samples for bacterial coinfections was significantly higher in ICU patients than in cases admitted to the other ward. They reported that the most common species were Acinetobacter baumannii and Klebsiella pneumoniae which were only susceptible to colistin. Their results highlighted the importance of the positive association between ICU admission in COVID-19 patients and the possibility of multidrug-resistant bacterial. It has been suggested that empiric antibiotic treatment should be considered in hospitalized patients with the following features; having serious underlying disease, immunocompromised cases, or radiographic or laboratory findings compatible with bacterial infection

- Fungal coinfections in ICU patients with covid-19
- The treatment target in patients with severe covid-19 was immunoregulatory agents such as corticosteroids to reduce the systemic inflammatory response to the virus . Consequently, covid-19 patients, especially immunocompromised and critically ill cases, were more suspected to be coinfected with opportunistic fungus. Several studies have been performed on the correlation between immunosuppressive treatment of covid-19 and the development of fungal coinfections; high-dose corticosteroids remarkably increased the risk of aspergillosis and candidemia in critically ill covid-19 patients.In addition, the risk of fungal pneumonia and sinusitis increased in covid-19 patients admitted to the ICU who received tocilizumab.

- In addition to immunosuppressants, intensive medical interventions, such as mechanical ventilation and central venous catheters, lead to fungal colonization and proliferation and predispose ICU patients to fungal coinfections. Detecting fungal contamination requires comprehensive diagnostic measures such as histopathology, direct microscopic examination, culture, β-D-glucan, galactomannan, and PCR-based assays .The diagnostic efficacy of these tests was practically different according to the fungal species. For example, a meta-analysis of published data estimated the specificity of PCR to be around 90% and of β-D-glucan to be around 80% for invasive candidiasis .Therefore, using more than one test in patients suspected of having a fungal infection has been suggested to improve the test's diagnostic efficacy. In the study the overall mortality rate in coinfection with covid-19 and fungi was estimated at 53%, significantly different from patients without fungal coinfection (31%). Echinocandins and azoles were the first-line antifungal agents to treat invasive fungal infections. However, treatment failure occurred in cases infected with multi-drug resistant Candida spp., such as C. auris and C. glabrata. So, screening for fungal infection in high-risk cases and maybe initiating prophylactic treatment could improve the management of covid-19 patients admitted to the ICU and their outcomes.

- Viral coinfections in ICU patients with covid-19
- The rate of coinfection with viruses among the Covid-19-positive population was significantly lower than that of the SARS-CoV-2-negetive population. It directly correlated with age and was higher in covid-19 patients aged 60. A systematic review of 33 published articles estimated the pool prevalence of viral infection among covid-19 patients to be 12.58%. They also found a high heterogeneous prevalence of viral coinfections in different geographic regions. They mentioned that blood-borne viruses were more common than respiratory viruses, and most cases (11.71%) were coinfected with Herpes virus. Also, treating patients who were positive for covid-19 and other viruses was more complicated; They are at a higher risk of progression to ARDS, and consequently, they need more extended hospitalization and ICU care than others. Thus, the possibility of viral coinfections, especially among immunocompromised patients, needs more attention during the covid-19 pandemic.
- The limitation of the present study was the limited published articles on this topic. According to the high prevalence of coinfection in covid-19 patients admitted to ICU and its relationship with the outcomes, the lack of a suitable study in this field, and the different methodologies in reporting the prevalence of pathogens, we could not compare the prevalence of pathogen types

- Data availability statement: All data from the current study are available from the corresponding author upon reasonable request.
- Funding statement: This study was funding by Isfahan university of medical sciences
- Conflict of interest disclosure: The authors declare that they have no competing interests

Table 1. Characteristics of included studies according to the prevalence and type of pathogens caused coinfection in ICU patients with covid-19

Author	Year	Country	Study design	Sample Size	Sex	Age	Type of pathogens	NI[*]	Prevalence	NIH score
Alhanthy [58]	2020	Saudi Arabia	Case report	1	M	25	Human metapneumovirus	-	-	-
Amaral [59]	2020	Brazil	Case report	1	M	62	Cytomegalovirus	-	-	-
Amarsy[60]	2021	France	Cross-sectional	12	F:4 M:8	56.8±15.6	Klebsiella pneumoniae	+	-	8:14
Amarsy [61]	2020	France	Cross-sectional	5	-	-	Serratia marcescens	+	-	5:14
Anderson [62]	2020	USA	Case report	1	M	49	Legionella pneumophila	-	-	-
AssaF[63]	2021	Egypt	Cross-sectional	40	M:32 F:8	59.3 ± 12.6	Klebsiella pneumoniae (10/20, 50%), Acinetobacter calcoaceticus baumanni complex (7/20, 35%) Enterobacter cloacae complex (5/20, 25%), Staphylococcus aureus (4 (MRSA)/20, 20%) Streptococcus agalactia (3/20, 15%) Haemophilus influenza (1/20, 5%) Klebsiella aerogenes (1/20, 5%) Escherichia coli (1/20, 5%) Streptococcus pneumoniae (1/20, 5%)	-	-	9:14
Bardi [14]	2021	Spain	Case-control	140	M: 77%	61	Gram-positive (55%) Gram negative bacteria (30%) Fungi (15%)	91 episodes of confirmed NI in 57 patients	-	8:12
Baskaran [64]	2021	UK	Cohort	254	M: 64.6%	59	coinfection/ co-colonisation: 83 (32.7%) Klebsiella spp. 16 (18.2%) Escherichia coli 20 (22.7%) Enterobacter aerogenes 5 (5.7%) Pseudomonas spp. 13 (14.8%) Serratia marcescens 1 (1.1%) Citrobacter koseri 5 (5.7%) Staphylococcus aureus 11 (12.5%) Haemophilus influenzae 4 (4.5%) Acinetobacter baumanii 2 (2.27%) Burkholderia multivorans 1 (1.1%) Enterococcus spp. 8 (9.1) Morganella morganii 1(1.1%) Raoultella sp. 1 (1.1%) Total 88	+	-	7:14
Bishburg [65]	2021	USA	Retrospective cohort	89	M:4 50%	63	Candidemia: 8 (8.9%) Tropicalis 2 (25%) Albicans 2 (25) Glabrata 2 (25) Parapsilosis 2 (25)	+	-	6:14
Bonazzetti [66]	2021	Italy	Retrospective observational study	89	M: 77.5%	61.5 yr; IQR, 53.1–68.7	60 patients (67.4%) experienced one or more of the 93 recorded BSI episodes 117 isolates: Gram-positive 85 (72.6%): Enterococcus faecalis26 (49.1%) Enterococcus hirae 1(1.8%) Coagulase-negative staphylococci (24, 20.5%) S. aureus (9, 7.6%) Gram-negative: Enterococcus species (53, 45.3%) Enterobacterales 24.8% Candida species 2.6%	+	-	7:14

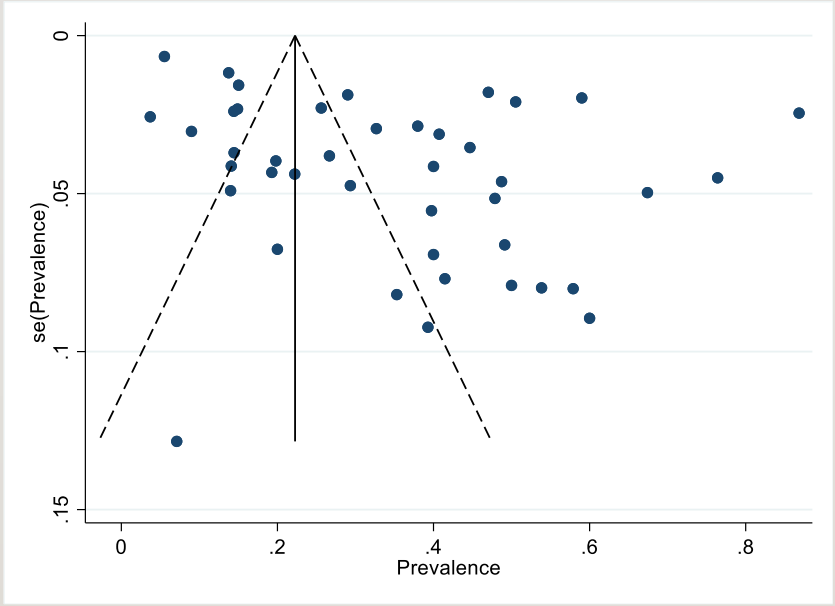

Figure 3. A funnel plot to check for the existence of publication bias in this study


THANKS FOR YOUR ATTENTION