University of Thi-Qar Journal of Science (UTJsci)
E-ISSN:2709-0256, ISSN Print: 1991-8690 Volume (10), No.1, June 2023

The Prevalence and Significance of the Pulmonary Bacterial Super-Infections among Hospitalized COVID-19 patients : A scoping Review

Muslim Dhahr Musa
Community Health Departement, Al-Nasiriyah Technical Institute / Southern Technical University
Thi-Qar / Iraq
Email: muslim1983@stu.edu.iq ,
ORCID:https://orcid.org/0000-0003-2648-400X,
Scopus Author ID: 57219161284

***Abstract*— Mortality of any respiratory viral disease is usually attributed in part to other reasons than the damaging effect of the virus alone. One of these reasons is the bacterial super-infection. For this reason, this scoping review attampts to evaluate the significant contribution of bacterial super-infection on the mortality among hospitalized COVID-19 patients and determine the true prevalence of bacterial super-infections in that population. Accordingly, a systematic search was employed with precise criteria on the MEDLINE, SCOPUS, PUBMED, and GOOGLE SCHOLAR databases published in the English language three years from January 2020 to January 2023. The prevalence of bacterial super-infection (BSI) among COVID-19 patients constitutes a point of contention among publications. This heterogeneity among publications came from the semantic dilemma of co-infection and super-infection.Co-infection was determined to be found in a relatively narrow range (1.2-3.1%), while prevalence of bacterial super-infection among COVID-19 patients varied from 18.2 to 50%. The bacterial super-infection significantly increases COVID-19 mortality, with the Odd ratio ranging from 1.76 to 10.53 [CI 95%]. Bacterial super-infection among hospitalized COVID-19 patients represents a non-recognized threat, especially during the first wave of the pandemic. The Prevalence of bacterial super-infection is comparable with those observed in previous influenza and SARS epidemics. A significant contribution of bacterial super-infection, especially the pulmonary to mortality of COVID-19 patients, was observed clearly**

Keywords— Bacterial superinfection, Prevalence, COVID-19, Hositalized patients.

I. INTRODUCTION

Three years ago, the world was taken aback by the new emerging viral disease caused by severe acute respiratory syndrome *Coronavirus* 2 (SARS-Cov-2) called COVID-19, which spread from Hubie-China like wildfire, reaching the pandemic level within a few weeks(World Health Organization, 2020). Many medical decisions have been made with very limited and no clinical experience or adequate scientific evidence, so typically, during such chaos situation, the attention is initially directed to the clinical management of the initial infection, neglecting the lurking threat behind the COVID-19, bacterial super-infection (BSI) that occurs after viral infection[2].

Many immune suppurative drugs (Tocilizumab) and broad-spectrum antibiotics were used worldwide, raising the question of how much bacterial infection is among those populations and the cost. The impacts of bacterial super-infection (BSI) during a respiratory viral epidemic can be viewed in three main points; firstly, it constitutes an important pressure factor on healthcare facilities by prolonging hospital stay and increasing the need for intensive care unit (ICU) admission [3], [4]. Secondly, associated with the worsening clinical outcome of viral pneumonia, this fact has been noticed during H5N1 Influenza and SARS pandemics. Many previous epidemiological studies stated that the BSI with respiratory viruses could significantly increase the pneumonia severity, which ultimately increases the mortality rate of viral pneumonia; the best example is the synergism between the influenza virus and *S.pneumonia* that account for the majority of death of influenza pandemic [5]–[8].

Thirdly, worsening the already horrible situation of antibiotic resistance globally. Such a situation was experienced during the previous pandemic of SARS during 2002-2003 as the rate of methicillin resistance of staphylococcus raised more than seven times that of pre-pandemic[9]. Due to difficulty distinguishing the clinical

https://doi.org/10.32792/utq/utjsci/v10i1.930

and radiological findings of viral pneumonia from those Klebsiella), it is difficult to rule out the bacterial co-infection or suer-infection at admission time, leading to a significant increase in the prescription of broad-spectrum antibiotics [10]. It has been stated that antibiotic usage (96-100%) in managing COVID-19 was much higher than the reported secondary bacterial infections among COVID-19 patients, especially during the first wave of the pandemic[11], [12].

Reviewing the documents of previous pandemics/epidemics shows that the effect of secondary bacterial infections can be described as inevitable. For example, 30-55% of 2009 H1NI Influenza deaths worldwide were due to the consequences of secondary bacterial infections[13], [14]. Indeed, half of the non-surviving COVID-19 patients were found to be secondary bacterial infection positive[11].

Studies regarding secondary bacterial infection during a respiratory viral epidemic are crucial for diagnosing, managing, and preventing these infections, planning for pandemic preparedness, and ensuring the wise use of antibiotics that minimize the risk of developing multidrug-resistant strains [15]. Previous documents have undertaken the prevalence, incidence, and identification of secondary bacterial pulmonary infection of SARS-Cov-2 patients; however, the contribution of secondary bacterial infection in the mortality of COVID-19 has not been well previously discussed. Similarly, most previous studies have not included the strength of the association of risk factors for pulmonary bacterial super-infection and prognostic value. Therefore, this review aimed to determine the prevalence and evaluate the secondary bacterial pulmonary caused by bacteria (Penumoniacoccal, Staphylococcal, and infection's associated outcome among hospitalized COVID-19 patients.

II. Methodology

This scoping review was conducted based on a comprehensive systematic search of MEDLINE, SCOPUS, PUBMED, and GOOGLE SCHOLAR databases published in the English language in the period of three years from January 2020 to January 2023, with the following different combinations of keywords; "Bacterial-super infection, COVID-19"/ or "bacterial co-infection of COVID19 patients" / or "COVID-19 patients with secondary bacterial infections"/or "Bacterial infection of COVID ICU patients."/ or SARS-Cov-2 super-infection /or “bacterial infection novel coronavirus” / or “covid-19 risk factors” /or "prediction of COVID”. Only those articles that met the inclusion criteria were considered in this review.

A. *Inclusion criteria*

1- Peer-reviewed research articles
2- The article included the CDC's definition of Super-infection
3- Articles that focused on pulmonary infection
4- Only patients with PCR-confirmed COVID-19

B. *Exclusion Criteria*

1- Short communication
2- Reviews
3- Letters
4- Correspondences
5- Unpublished or not peer-reviewed articles
6- Case study

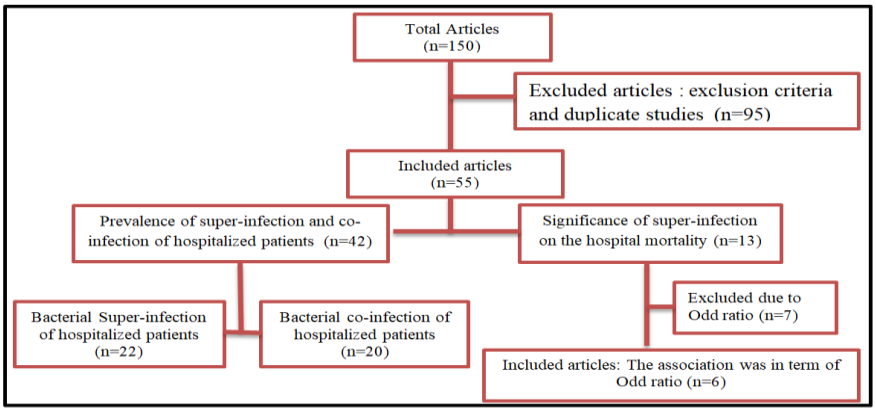

Figure (1)flow chart for studies included and screening procedure.

III. Prevalence of Bacterial Super-infection in Hospitalized COVID-19 Patients

Measuring the proportion of COVID-19 patients with SBI is critical to inform us as to how extent the bacterial infections are spreading among COVID-19 patients, which hopefully helps minimize the overuse of antibiotics and to estimate the contribution of SBI in the worsening of the clinical outcome. The prevalence of SBI among COVID-19 patients constitutes a point of contention among publications. Previous meta-analysis reviews reported high heterogeneity (I^2 ranging from 92-49%) among studies [16], [17]. Notably, this heterogeneity among publications came from the semantic dilemma of co-infection and super-infection[16]. Many authors failed to correctly use those terms, which reflected an underestimation or overestimation of the SBI among COVID-19 patients.

In this review, the most acceptable CDC definition of co-infection and secondary/super-infection will be considered; a co-infection coincides with the primary infection or concomitant infection roughly identified within the first 48 of hospital admission, while secondary/super-infection is defined as those infections that occur after the

initial infection (diagnosed in >48hours). Usually, the causative agent of super-infection exhibits antibiotics resistant to previously used antibiotics (18). Bacterial co-infection at the time of hospital admission is usually associated with an increase the clinical severity and death[7]; however, in the COVID-19 pandemic, the prevalence of bacterial co-infection was determined to be found in a relatively narrow range (1.2-3.1%) in studies that clearly defined co-infection[18]–[22] based on CDC definition. A good explanation of the low co-infection rate during the COVID-19 pandemic in comparison with the previous pandemic (H1N1, SARS) was speculated by Garcia-Vidal and his colleagues [20], the macrophage hyper-activation had some role in lowering the co-infection in addition to accumulative experience from previous pandemics as empirical antibiotics therapy begins at early hospital admission. More recently, A few studies (all published in 2022) recorded rates of bacterial co-infection out of that range like Coenen *et al.* [23], who reported 12.4%, and Bolker *et al.* reported 11.2[24] Cohen *et al.* reported 60% it is seems that the Prevalence of bacterial co-infection raised during 2022. Only Zhua and his colleagues were an outlier as they reported that 91.8% (236/242) had bacterial co-infection at admission time [25]. Nevertheless, it appears that estimation of the true prevalence of bacterial co-infection based on the previous studies is almost impossible since all these studies were conducted retrospectively during the first or second wave of the pandemic when the major focus was directed against the primary viral infection and no bacteriological tests performed at the time of admission. Thus it is believed that bacterial co-infection went underestimated.

On the other hand, super-infections are relatively prevalent, particularly in severely ill patients. All studies concerning the super-infections showed that the Prevalence of bacterial super-infection among COVID-19 patients varied from 18.2 to 50%[26]–[33]. However, the prevalence can be higher in some studies; in Egypt, Takwa et al., 2020 reported 100%[34] and in Iran, said 95%[35],[33]. Interestingly, super-infection is exclusively recorded in the intensive care unit (ICU), particularly in the later phase of ICU admission, indicating a direct association with the length of ICU stay[20], [29]. In a closer look at the association between ICU stay and incidence of super-infections, it can be speculated that some unique and extra risk factors directed upon patients in the ICU settings include; massive administration of immunosuppressive drugs (tocilizumab and corticosteroids), mechanical ventilation, the exhausted immune response of ICU patients. Additionally, ICU wards were usually overcrowded at more than 350% of their original capacity during the peaks of the outbreak, which necessitated the translocation of healthcare workers that were ordinarily not practiced to work in the ICU settings leading to an increase in super-infections in the ICU wards[36]. However, the true prevalence of BSI has usually been underestimated because of the competing risk of death during early ICU admission, which might occur before SBI development[31].

IV. Pathogenesis of Bacterial-Super infection (Viral-Bacterial interaction)

The role of bacterial infections in the pathogenesis of the infectious disease caused by a newly emerging respiratory virus is usually not fully understood. Viral infections, particularly respiratory tract infections, are frequently followed by bacterial infections of the virus-affected organ, associated with high morbidity and mortality. However, two general forms of bacterial-viral interactions worsen the disease outcome; the direct form, in which the virus takes advantage of bacterial components to facilitate cell penetration, and the indirect form, which include the consequences of viral infection that increase bacterial pathogenicity [37].

Much of what we know so far comes from animal model studies demonstrating that complex molecular mechanisms underpin a virus's ability to predispose to bacterial infection. Resolving the virus-induced inflammatory process opens a window of a period (7-14 days) during which the susceptibility for bacterial super-infection is usually high (25). Two mechanisms are involved in the predisposition for bacterial infection during this period (window of susceptibility); the mechanical mechanism, which enhances bacterial adhesion and colonization, and the immunological mechanism, which enhances bacterial pathogenicity[38].

Respiratory viral infections cause cell death and disrupt mucins, exposing new attachment sites for bacteria [39]. Previous research on influenza virus A, demonstrated by Peltola et al. (2006)[40], showed the colonization rate of *S. pneumonia* of airways increased significantly in animal models (Ferrets) after being experimentally infected with H3N2 subtype influenza A. The bacterial adhesion is enhanced by virus activation of Tumor Growth Factor beta (TGF-β), which up-regulates the expression of fibronectin and integrins (bacterial receptor on mammalian cells)[41]. Because of its sialidase activity, the influenza virus neuraminidase can alter the carbohydrate moieties on the surface of mammalian cells exposing new bacterial receptors[42], [43]. Similarly, respiratory syncytial virus (RSV) glycoprotein expressed on the surface of infected cells acts as a receptor for pneumococci[44]. Surface glycoprotein adhesion molecule-1 (ICAM-1) has been shown to have up-regulated expression during RSV and viral infection. ICAM-1 was recognized as a cognate ligand for the non-typeable H. influenza Type IV pilus. It is proposed that the immune response during viral infection opens new bacterial attachments sites by upregulation in the expression of receptor molecules used by bacteria, as illustrated by Cundell et al. that increased performance of the G-protein-coupled platelet-activating factor (PAF) is utilized by some bacteria such as *S. pneumoniae* for their attachment and colonization in the endothelial cells[45]. The ciliary function of respiratory cells is impaired by virus infection which ultimately lead to decrease the clearance of inspired bacteria[46].

On the other hand, the immunological mechanism is marked by impaired antibacterial effector function of myeloid immune cells [47]–[49]. Studies of the influenza virus showed the loss or dysfunction of innate immune effectors cells, particularly neutrophils, and macrophages, causing poor control of bacterial infection[38]. Recently,

several studies have proposed the term " Emergency myelopoiesis," which describes the immune response to a severe viral infection that induces a progenitor bone marrow in the predisposing for bacterial super-infection is demonstrated by the great work of Shambat and his colleagues, as they found that critically ill patients with acute COVID-19 had altered neutrophil and monocyte effector cytokines, which hindered their ability to respond to bacterial challenges. His findings suggest that acute COVID-19 is characterized by immature hyper-activated, dysfunctional neutrophils and monocytes with reduced effector responses like; reduced production of reactive oxygen species and myeloperoxidase upon secondary bacterial challenge.

Similarly, Peyneau et al. 2022[50] found that the antimicrobial activity of neutrophils and monocytes (phagocytosis, oxidative burst, and netosis) is initially hyper-activated but decreased capacity to reactivate, rendering the OCVID-19 patients with a great susceptibility to microbial infection. The impaired myeloid cell functions are significantly higher in ICU patients than Non-ICU. Additionally, the dysfunctional myeloid cells have immunosuppressive characteristics, resulting in reduced lymphoid cell count in the later stages of severely hospitalized COVID patients[12]. A direct association of the SARS-Cov-2 mediated hypercytokinemia and bacterial cell to massive production of suppressive immature neutrophils during the severe course of COVID-19 disease[49]. The contribution of immunological mechanism super-infection. Significant inflammatory cytokines were observed primarily in COVID-19 patients with bacterial super-infection[49].

V. The significance of pulmonary bacterial super-infection in the mortality of COVID-19 patients

Initially, looking at the risk factors regarding COVID-19 mortality is essential**.** Previous studies concerning the mortality of CVID-19 have stated many risk factors, including age, sex, comorbidities, severe clinical feature at admission, length of ICU stay, obesity, and elevated level of CRP[51], [52]. However, a thorough assessment of the extent to which these risk factors contribute to COVID-19 mortality, or at the very least, how to prioritize these risk factors, has not been disclosed. In this review, the major focus will be on bacterial super-infection. Among the risk factors mentioned above, it is obvious that the mortality of COVID-19 is governed by two reciprocally feeding risk factors, namely, the severity at presentation and bacterial super-infection. Figure (2) organizing the most studied risk factors of COVID-19 mortality.

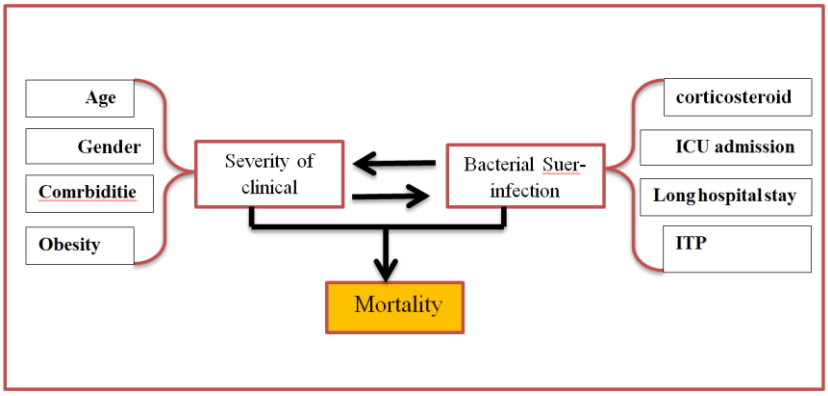

Figure (2): orginazation the various COVID-19 mortality associated risk factors. ICU: Intense Care Unit, ITP: Invasive Therauetic Procedure

Previous studies have mentioned various risk factors for pulmonary bacterial super-infection among hospitalized COVID-19 patients. Nevertheless, the identified risk factors are the acute initial clinical figure at presentation (Bardi et al., 2021; Nasir et al., 2021), corticosteroid administration[53], and the use of invasive therapeutic procedures such as an endotracheal tube, central venous catheters(Buehler et al., 2021), admission to ICU (Søvik, S et al. 2022) and length of hospital stay, particularly in ICU. On the other hand, the severity of clinical features at admission, which is the second player of mortality, is thrived by older age, gender, and comorbidities. For age, most studies agreed that age >60 years constitutes an important risk of severe clinical presentation due to impaired immunity as those patients have reduced production of T and B cells as well as reduced innate immunity, which alters the viral clearance in addition to dysregulating immune cells that produce large quantities of cytokines culminated by a cytokine storm[54], [55]. Older age was also implicated as a predictor of ICU admission with an odd ratio (3.28, [1.71-6.25])[56]. Similarly, almost all previous studies regarding mortality risk factors accounted for those comorbidities independently associated with a severe form of COVID-19, ultimately leading to death[55], [57]–[59]. Regarding the gender differences, females may have the advantage of COVID-19 resistance as females' adaptive immune responses have higher CD4 and CD8 T-cells than males. Additionally, the essintial immune regulatory genes are located on chromosome X, and females have a higher level of TL7 expression than males(Abdullah et al. 2012).

The role of super-infection in COVID-19 was evidenced based on the previous respiratory epidemic (Influenza). However, many previous kinds of research and review articles have undertaken the role of bacterial super-infection in the severity of COVID-19. It is interesting to find the role of BSI in the mortality of hospitalized COVID-19. Previous studies have mentioned the BSI as a significant mortality prognostic factor, in addition to older age, the high level of D-dimer, and sequential organ failure assessment (SOFA) (Zhou P, 2020). The bacterial super-infection appears to significantly increase COVID-19 mortality, with the Odd

ratio ranging from 1.76 to 10.53, as presented in Table (1). Italy found an increase in the super-infection rate from 21.7% to 57.6% during ICU stay. Additionally, most studies found that the association of bacterial super-infections with mortality of COVID-19 patients was around 35%, exceeding other prognostic factors(Bardi et al., 2021; Nasir et al., 2021; Shafran et al., 2021). The death rate associated with bacterial super-infection in COVID-19 was significantly higher than in the Influenza patients group (Shafran et al., 2021).

Table (1): studies regarding the association of bacterial super-infections to COVID-19 mrtality exressed in term of odd ration

Reference	Odd ratio	Study population
[61]	4.42(1.63-11.9)	100
[56]	2.54 (1.056.18)	590
[36]	2.7(1.2-5.9)	140
[62]	3.720 (1.992-6.950)	410
[63]	2.80(1.98-4.02)	1398
[58]	7.2 (4.25-9.05)	173

VI. Conclusions

Bacterial super-infection among hospitalized COVID-19 patients represents a non-recognized threat, especially during the first wave of the pandemic. The prevalence of bacterial super-infection is comparable with those observed in previous influenza and SARS epidemics. A significant contribution of bacterial super-infection, especially the pulmonary to mortality of COVID-19 patients, was observed clearly in the previous studies.

VII. Limits of the review

In this review, some studies concerning the prevalence of bacterial super-infection were included, although there was no clear discrimination between the bacterial super-infection from colonization based on the CDC definition. Only studies conducting bacterial culture or PCR to detect bacterial infection in pulmonary samples were considered in this review. Similarly, concerning the Prevalence of secondary bacterial infection, that range only represents the prevalence in ICU patients.

References

[1] World Health Organization (WHO), "Coronavirus disease 2019 (COVID-19) Situation Report – 51," 2020.

[2] J. Li *et al.*, "Etiology and antimicrobial resistance of secondary bacterial infections in patients hospitalized with COVID-19 in Wuhan, China: a retrospective analysis," *Antimicrob. Resist. Infect. Control*, vol. 9, no. 1, pp. 1–7, 2020, doi: 10.1186/s13756-020-00819-1.

[3] R. Mirzaei *et al.*, "Bacterial co-infections with SARS-CoV-2," *IUBMB Life*, vol. 72, no. 10, pp. 2097–2111, 2020, doi: 10.1002/iub.2356.

[4] Z. L. Esper FP, Spahlinger T, "Rate and influence of respiratory virus coinfection on pandemic (H1N1) influenza disease," *J Infect*, vol. 63, pp. 260–266, 2011.

[5] J. L. D. Pozo, "Respiratory co-and superinfections in covid-19," *Rev. Esp. Quimioter.*, vol. 34, pp. 69–71, 2021, doi: 10.37201/req/s01.20.2021.

[6] C. Beadling and M. K. Slifka, "How do viral infections predispose patients to bacterial infections?," *Curr. Opin. Infect. Dis.*, vol. 17, no. 3, pp. 185–191, 2004, doi: 10.1097/00001432-200406000-00003.

[7] et al. Martín-Loeches I, Sanchez-Corral A, Diaz E, Granada RM, Zaragoza R, Villavicencio C, "Community-acquired respiratory coinfection in critically ill patients with pandemic 2009 influenza A(H1N1) virus," *Chest.*, vol. 139, no. 3, pp. 555–63, 2011.

[8] C. S. Morris DE, Cleary DW, "Secondary bacterial infections associated with influenza pandemics," *Front Microbiol.*, vol. 8, no. 1041, 2017, doi: 10.3389/fmicb.2017.01041.

[9] F. H. Y. Yap *et al.*, "Increase in methicillin-resistant Staphylococcus aureus acquisition rate and change in pathogen pattern associated with an outbreak of severe acute respiratory syndrome," *Clin. Infect. Dis.*, vol. 39, no. 4, pp. 511–516, 2004, doi: 10.1086/422641.

[10] V. Chibabhai, A. G. Duse, O. Perovic, and G. A. Richards, "Collateral damage of the COVID-19 pandemic: Exacerbation of antimicrobial resistance and disruptions to antimicrobial stewardship programmes?," *South African Med. J.*, vol. 110, no. 7, pp. 572–573, 2020, doi: 10.7196/SAMJ.2020.V110I7.14917.

[11] F. Zhou *et al.*, "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study," *Lancet*, vol. 395, no. 10229, pp. 1054–1062, 2020, doi: 10.1016/S0140-6736(20)30566-3.

[12] C. Huang *et al.*, "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China," *Lancet*, vol. 395, no. 10223, pp. 497–506, 2020, doi: 10.1016/S0140-6736(20)30183-5.

[13] M. 2009 United States, "Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1)-United States, May-August 2009.," vol. 58, no. 38, pp. 1071–4, 2009.

[14] V. C. Weinberger DM, Simonsen L, Jordan R, Steiner C, Miller M, "Impact ofthe 2009 influenza pandemic on pneumococcal pneumonia hospitalizations inthe United States.," *J Infect Dis*, vol. 205, no. 3, pp. 458–465, 2012.

[15] B. D. Huttner, G. Catho, J. R. Pano-Pardo, C. Pulcini, and J. Schouten, "COVID-19: don't neglect antimicrobial stewardship principles!," *Clin. Microbiol. Infect.*, vol. 26, no. 7, pp. 808–810, 2020, doi: 10.1016/j.cmi.2020.04.024.

[16] B. J. Langford *et al.*, "Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis," *Clin. Microbiol. Infect.*, vol. 26, no. 12, pp. 1622–1629, 2020, doi: 10.1016/j.cmi.2020.07.016.

[17] L. Lansbury, B. Lim, V. Baskaran, and W. S. Lim, "Co-Infections in People with COVID-19: A

Systematic Review and Meta-Analysis," *SSRN Electron. J.*, no. January, 2020, doi: 10.2139/ssrn.3594598.

[18] L. Wang *et al.*, "An observational cohort study of bacterial co-infection and implications for empirical antibiotic therapy in patients presenting with COVID-19 to hospitals in North West London," *J. Antimicrob. Chemother.*, vol. 76, no. 3, pp. 796–803, 2021, doi: 10.1093/jac/dkaa475.

[19] S. Vijay *et al.*, "Secondary infections in hospitalized COVID-19 patients: Indian experience," *Infect. Drug Resist.*, vol. 14, pp. 1893–1903, 2021, doi: 10.2147/IDR.S299774.

[20] C. Garcia-Vidal *et al.*, "Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study," *Clin. Microbiol. Infect.*, vol. 27, no. 1, pp. 83–88, 2021, doi: 10.1016/j.cmi.2020.07.041.

[21] Z. Karami *et al.*, "Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalized patients with COVID-19: results from a multicentre retrospective cohort study in The Netherlands," *Infect. Dis. (Auckl).*, vol. 53, no. 2, pp. 102–110, 2021, doi: 10.1080/23744235.2020.1839672.

[22] T. Lardaro *et al.*, "Characteristics of COVID-19 patients with bacterial coinfection admitted to the hospital from the emergency department in a large regional healthcare system," *J. Med. Virol.*, vol. 93, no. 5, pp. 2883–2889, 2021, doi: 10.1002/jmv.26795.

[23] S. Coenen *et al.*, "Low frequency of community-acquired bacterial co-infection in patients hospitalized for COVID-19 based on clinical, radiological and microbiological criteria: a retrospective cohort study," *Antimicrob. Resist. Infect. Control*, vol. 10, no. 1, pp. 1–10, 2021, doi: 10.1186/s13756-021-01024-4.

[24] A. Bolker, K. Coe, J. Smith, K. Stevenson, S. Wang, and E. Reed, "Predictors of respiratory bacterial co-infection in hospitalized COVID-19 patients," *Diagn. Microbiol. Infect. Dis.*, vol. 102, 2022.

[25] F. Z. Xiaojuan Zhua, Yiyue Gea, Tao Wua, Kangchen Zhaoa, Yin Chena, Bin Wua and L. C. Baoli Zhua, b, "Co-infection with respiratory pathogens among COVID-2019 cases," *Virus Res.*, vol. 285, p. 198005, 2020.

[26] J. C. Cataño-Correa, J. A. Cardona-Arias, J. P. P. Mancilla, and M. T. García, "Bacterial superinfection in adults with COVID-19 hospitalized in two clinics in Medellín-Colombia, 2020," *PLoS One*, vol. 16, no. 7 July, pp. 1–12, 2021, doi: 10.1371/journal.pone.0254671.

[27] P. K. Buehler *et al.*, "Bacterial pulmonary superinfections are associated with longer duration of ventilation in critically ill COVID-19 patients," *Cell Reports Med.*, vol. 2, no. 4, 2021, doi: 10.1016/j.xcrm.2021.100229.

[28] T. Pan, D. Chen, Y. Chen, and Z. Lin, "Clinical Features and Risk Factors for Secondary Infection in Critically Ill Patients With COVID-19," pp. 1–17.

[29] P. B. Rafael Ramosa, Sofía de la Villab, Sergio García-Ramosa, Belén Padillab, Pablo García-Olivaresc, Patricia Pi˜neroa, Alberto Garridoc, Javier Hortala, Patricia Mu˜nozb, d, Estrela Caama˜noa, "COVID-19 associated infections in the ICU setting: A retrospective analysis in a tertiary-care hospital," *Enferm. Infecc. Microbiol. Clin.*, vol. xxx, no. xxx, pp. 19–21, 2020.

[30] C. O. Pickens *et al.*, "Bacterial superinfection pneumonia in patients mechanically ventilated for COVID-19 pneumonia," *Am. J. Respir. Crit. Care Med.*, vol. 204, no. 8, pp. 921–932, 2021, doi: 10.1164/rccm.202106-1354OC.

[31] C. C. Battaglia and K. Hale, "Hospital-Acquired Infections in Critically Ill Patients With Cancer," *J. Intensive Care Med.*, vol. 34, no. 7, pp. 523–536, 2019, doi: 10.1177/0885066618788019.

[32] M. Giacomo Grasselli, MD; Vittorio Scaravilli, MD; Davide Mangioni, MD; Luigia Scudeller, MD; Laura Alagna *et al.*, "Hospital-Acquired Infections in Critically Ill Patients With COVID-19," *Chest*, vol. 160, no. 2, pp. 454–465, 2021.

[33] H. K. A. Ramadan *et al.*, "Predictors of severity and co-infection resistance profile in COVID-19 patients: First report from upper Egypt," *Infect. Drug Resist.*, vol. 13, pp. 3409–3422, 2020, doi: 10.2147/IDR.S272605.

[34] R. H. A. Takwa E. Meaweda, Sherweet M. Ahmedb, Sherif M.S. Mowafyc, Ghada M. Samird, "Bacterial and fungal ventilator associated pneumonia in critically ill COVID-19 patients during the second wave," *J. Infect. Public Health*, 2020.

[35] E. Sharifipour *et al.*, "Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU," *BMC Infect. Dis.*, vol. 20, no. 1, pp. 1–7, 2020, doi: 10.1186/s12879-020-05374-z.

[36] T. Bardi *et al.*, "Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome," *Eur. J. Clin. Microbiol. Infect. Dis.*, vol. 40, no. 3, pp. 495–502, 2021, doi: 10.1007/s10096-020-04142-w.

[37] S. Manna, P. Baindara, and S. M. Mandal, "Molecular pathogenesis of secondary bacterial infection associated to viral infections including SARS-CoV-2," *J. Infect. Public Health*, vol. 13, no. 10, pp. 1397–1404, 2020, doi: 10.1016/j.jiph.2020.07.003.

[38] C. Paget and F. Trottein, "Mechanisms of bacterial superinfection post-influenza: A role for unconventional T cells," *Front. Immunol.*, vol. 10, no. MAR, 2019, doi: 10.3389/fimmu.2019.00336.

[39] Bakaletz LO, "Viral-bacterial co-infections in the respiratory tract," *Curr Opin Microbiol*, vol. 35, pp. 30–35, 2017.

[40] V. T. Peltola, K. L. Boyd, J. L. McAuley, J. E. Rehg, and J. A. McCullers, "Bacterial sinusitis and otitis media following influenza virus infection in ferrets," *Infect. Immun.*, vol. 74, no. 5, pp. 2562–2567, 2006, doi: 10.1128/IAI.74.5.2562-2567.2006.

[41] W. B. Li N, Ren A, Wang X, Fan X, Zhao Y, Gao GF, Cleary P, "Influenza viral neuraminidase primes

bacterial coinfection through TGF-beta-mediated expression of host cell receptors.," *Proc Natl Acad Sci U S A*, vol. 112, pp. 238–242, 2015.

[42] S. T. Ballinger MN, "Postinfluenza bacterial pneumonia: host defenses gone awry," *J Interf. Cytokine Res*, vol. 30, pp. 643–652, 2010.

[43] McCullers JA, "The co-pathogenesis of influenza viruses with bacteria in the lung," *Nat Rev Microbiol*, vol. 12, pp. 252–262, 2014.

[44] M. J. Iverson AR, Boyd KL, McAuley JL, Plano LR, Hart ME, "Influenzavirus primes mice for pneumonia from Staphylococcus aureus," *J Infect Dis*, vol. 203, no. 6, pp. 880–8., 2011.

[45] T. E. Cundell DR, Gerard NP, Gerard C, Idanpaan-Heikkila I, "Strep-tococcus pneumoniae anchor to activated human cells by the receptor forplatelet-activating factor.," *Nature*, vol. 377, no. 6548, pp. 435–8, 1995.

[46] H. A. Pittet LA, Hall-Stoodley L, Rutkowski MR, "Influenza virus infection decreases tracheal mucociliary velocity and clearance of Streptococcus pneumoniae.," *Am J Respir Cell Mol Biol*, vol. 42, pp. 450–460, 2010.

[47] et al Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, "Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure," *Cell Host Microbe*, vol. 27, no. 6, pp. 992–1000, 2020.

[48] L. D. He Y, Li W, Wang Z, Chen H, Tian L, "Nosocomial infection among patients with COVID-19: A retrospective data analysis of 918 cases from a single center in Wuhan, China," *nfect Control Hosp Epidemio*, vol. 41, no. 8, pp. 982–983, 2020.

[49] S. M. Shambat *et al.*, *Hyperinflammatory environment drives dysfunctional myeloid cell effector response to bacterial challenge in COVID-19*, vol. 18, no. 1. 2022.

[50] M. Peyneau *et al.*, "Innate immune deficiencies are associated with severity and poor prognosis in patients with COVID-19," *Sci. Rep.*, vol. 12, no. 1, pp. 1–11, 2022, doi: 10.1038/s41598-021-04705-7.

[51] M. A. Abolfotouh, A. Musattat, M. Alanazi, S. Alghnam, and M. Bosaeed, "Clinical characteristics and outcome of Covid-19 illness and predictors of in-hospital mortality in Saudi Arabia," *BMC Infect. Dis.*, vol. 22, no. 1, pp. 1–11, 2022, doi: 10.1186/s12879-022-07945-8.

[52] A. M. Cueto-Manzano *et al.*, "Risk factors for mortality of adult patients with COVID-19 hospitalised in an emerging country: A cohort study," *BMJ Open*, vol. 11, no. 7, pp. 1–9, 2021, doi: 10.1136/bmjopen-2021-050321.

[53] L. A. Ritter *et al.*, "The Impact of Corticosteroids on Secondary Infection and Mortality in Critically Ill COVID-19 Patients," *J. Intensive Care Med.*, vol. 36, no. 10, pp. 1201–1208, 2021, doi: 10.1177/08850666211032175.

[54] Y. Nlandu *et al.*, "Predictors of mortality in COVID-19 patients at Kinshasa Medical Center and a survival analysis: a retrospective cohort study," *BMC Infect. Dis.*, vol. 21, no. 1, pp. 1–11, 2021, doi: 10.1186/s12879-021-06984-x.

[55] A. Khan *et al.*, "Risk factors associated with worse outcomes in COVID-19: A retrospective study in Saudi Arabia," *East. Mediterr. Heal. J.*, vol. 26, no. 11, pp. 1371–1380, 2020, doi: 10.26719/emhj.20.130.

[56] B. Davido *et al.*, "Superinfection is associated with short-term outcome and mortality in viral respiratory tract infections during the fall-winter seasons 2016-2018 in the Greater Paris area: the SUPERFLUOUS study: outcomes of viral infections," *Int. J. Infect. Dis.*, vol. 119, pp. 217–224, 2022, doi: 10.1016/j.ijid.2022.04.008.

[57] A. Pramono, Y. B. Setiawan, and N. Maryani, "Risk Factors for Mortality in Indonesian COVID-19 Patients," *Open Access Maced. J. Med. Sci.*, vol. 9, no. T5, pp. 181–184, 2022, doi: 10.3889/oamjms.2021.7826.

[58] H. H. Assal *et al.*, "Predictors of severity and mortality in COVID-19 patients," *Egypt. J. Bronchol.*, vol. 16, no. 1, 2022, doi: 10.1186/s43168-022-00122-0.

[59] B. Bepouka *et al.*, "Risk factors for mortality in COVID-19 patients in sub-Saharan Africa: A systematic review and meta-analysis," *PLoS One*, vol. 17, no. 10 October, pp. 1–18, 2022, doi: 10.1371/journal.pone.0276008.

[60] V. S. bdullah M, Chai P-S, Chong M-Y, Tohit ERM, Ramasamy R, Pei CP, "Gender efect on in vitro lymphocyte subset levels of healthy individuals," *Cell Immunol.*, vol. 272, no. 2, pp. 2014–9, 2012.

[61] N. Nasir, F. Rehman, and S. F. Omair, "Risk factors for bacterial infections in patients with moderate to severe COVID-19: A case-control study," *J. Med. Virol.*, vol. 93, no. 7, pp. 4564–4569, 2021, doi: 10.1002/jmv.27000.

[62] I. W. Suranadi, I. M. A. K. Sucandra, N. N. D. Fatmawati, and A. D. F. Wisnawa, "A Retrospective Analysis of the Bacterial Infections, Antibiotic Use, and Mortality Predictors of COVID-19 Patients," *Int. J. Gen. Med.*, vol. 15, no. April, pp. 3591–3603, 2022, doi: 10.2147/IJGM.S351180.

[63] H. Scott, A. Zahra, R. Fernandes, B. C. Fries, H. C. T. Jr, and A. J. Singer, "Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information ," no. January, 2020.docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10