Sepsis Mortality Rates are Higher in Patients Hospitalized for COVID-19 Than for Influenza

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Patients hospitalized with COVID-19 are more likely to develop sepsis and septic shock when compared to patients admitted with influenza during the 2016, 2017, or 2018 flu seasons, according to EHR data.

Sepsis is defined as a clinical condition of life-threatening organ dysfunction caused by an abnormal response to infection. Septic shock is a subset of sepsis involving a severe decrease in blood pressure and other metabolic abnormalities, presenting a greater risk of death than with sepsis alone.[1] Early studies identified a high incidence of sepsis in patients with COVID-19.[2,3] Pathophysiologic investigations have pointed to viral sepsis as a serious manifestation of disease in COVID-19 patients.[4-6] To explore the incidence of sepsis in COVID-19 compared to other viral illnesses, we examined data from patients who were admitted to the hospital during their COVID-19 illness (n=66,236) and data from patients who were admitted for influenza during the influenza season in 2016, 2017, or 2018 (n=56,896). The incidence of sepsis, septic shock, and inpatient mortality are reported for each population in Table 1 below.

Table 1. Incidence and Outcomes of Sepsis by Disease

	COVID-19	Influenza
Total Patients	66,236	56,896
Sepsis Rate	32.3%	28.2%
Septic Shock Rate	10.1%	5.1%
Inpatient Mortality	15.8%	4.1%

	COVID-19	Influenza
Total Sepsis Patients	21,404	16,046
Sepsis Inpatient Mortality	31.5%	9.4%

	COVID-19	Influenza
Total Septic Shock Patients	6,719	2,923
Septic Shock Inpatient Mortality	59.4%	31.9%

Among hospitalized patients, overall inpatient mortality incidence was much higher in patients with COVID-19 (15.8%) than influenza (4.1%). The incidence of sepsis and septic shock were also higher in the COVID-19 population. In order to better understand the magnitude of this, we modelled the association between sepsis or septic shock and COVID-19, controlling for age and sex. Hospitalized patients with COVID-19 are 22% more likely to develop sepsis, and 113% more likely to develop septic shock compared to hospitalized patients with influenza (Table 2).

Table 2. Odds Ratios for Sepsis and Septic Shock for COVID-19 Patients Compared to Influenza

	Odds Ratio (95% CI)
Sepsis Risk	1.22 (±0.03)
Septic Shock Risk	2.13 (±0.10)

The odds ratios for sepsis and septic shock were calculated using a logistic regression model that controlled for age and sex.

In response to these findings, physicians should be vigilant and use all available resources in the early detection and treatment of sepsis in patients with COVID-19. Additional research would be beneficial to identify the risks for sepsis in COVID-19, the mechanisms of its development, and the optimal approaches to management.

This study was completed by two teams each comprised of a clinician and two research scientists who worked independently analyzing the risk of sepsis between patients with COVID-19 and those with influenza. The two teams came to similar conclusions. Data are pooled from 83 healthcare organizations representing 358 hospitals that span 47 states and cover 52 million patients.

Data Definitions

Term	Definition
Patient Sex	Patient's legal sex. Possible values include "Male," "Female," and "Other."
Patient Age Group	Patient's age in years. For the influenza cohorts, this is the patient's age at the time they had the virus.
Positive COVID-19 Lab Result	A final result for one of the lab components identified by individual health systems for SARS-CoV-2 with a "positive" value, as identified by the health systems. **Positive/Start Date:** Date the test was collected/performed
COVID-19 Diagnosis	The following code in one of the listed diagnosis settings. **Diagnosis Code:** U07.1 (ICD-10-CM) **Diagnosis Setting:** Encounter Diagnosis, Billing Diagnosis, Problem List **Start Date:** Diagnosis noted date or encounter start date

Term	Definition
COVID-19 Positive Patient	Patient with a positive SARS-CoV-2 lab result or a COVID-19 diagnosis. **Start Date:** The earlier of the earliest positive SARS-CoV-2 lab result collection date or earliest diagnosis noted date. If an inpatient admission began in the 7 days prior to this date, the admission date is used instead.
COVID-19 Related Admission	A hospital admission during which the patient had a positive SARS-CoV-2 lab test or COVID-19 diagnosis, OR a hospital admission with any respiratory diagnosis which happened within 42 days following the patient's COVID-19 start date. This excludes patients with nosocomial COVID-19. **Respiratory Diagnosis Codes:** J00-J99 (ICD-10-CM)
COVID-19 Related Inpatient Death	A COVID-19 related hospitalization with a discharge disposition of deceased or a death date on or before the discharge date.
Positive Influenza Lab Result	A final result for one of the lab components identified by individual health systems for influenza with a "positive" or "detected" value. LOINC codes include: 40982-1, 34487-9, 5866-9, 5862-8, 43874-7, 43895-2, 72365-0, 31859-2, 82170-2, 82166-0, 24015-0, 5230-8, 5229-0, 31864-2, 46082-4, 72366-8, 46083-2, 49524-2, 49521-8, 55465-9, 72367-6, 76078-5, 5863-6, 76080-1, 5867-7, 62462-7, 44575-9, 22827-0, 80382-5, 80383-3, 77028-9, 44564-3, 49534-1, 77027-1, 77026-3, 44563-5, 80590-3, 6437-8, 82169-4, 82167-8, 44577-5, 61102-0, 60494-2, 85477-8, 85478-6, 82168-6, 72356-9, 40981-3, 49531-7, 44573-4, 44560-1, 6604-3, 80588-7, 80591-1, 80589-5, 49523-4, 49520-0, 44567-6, 33535-6, 5864-4, 31858-4, 38381-0, 48509-4, 53251-5, 38382-8, 5861-0, 5865-1, 44559-3, 44572-6, 48310-7, 49535-8, 44263-2, 17015-9 **Positive/Start Date:** Date the test was collected/performed
Influenza Diagnosis	One of the following codes in one of the listed diagnosis settings. **Diagnosis Code:** J09, J10, J11 (ICD-10-CM), 6142004 (SNOMED), with the exception of diagnoses that use the words "influenza-like." **Diagnosis Setting:** Encounter Diagnosis, Billing Diagnosis, Problem List **Start Date**: Diagnosis noted date
Influenza Positive Patient	Patient with a positive influenza lab result or an influenza diagnosis. **Start Date:** The earlier of the earliest positive influenza lab result collection date, or the earliest influenza diagnosis noted date.
Influenza Related Admission	A hospital admission during which the patient had a positive influenza lab test or diagnosis, OR a hospital admission which happened within 14 days following the patient's influenza start date with a respiratory diagnosis code associated. **Respiratory Diagnosis Codes:** J00-J99 (ICD-10-CM)
Influenza Related Inpatient Death	An influenza related hospitalization with a discharge disposition of deceased or a death date on or before the discharge date.

Term	Definition
Influenza Season	The influenza season for each year is defined by CDC's FluView.[7] **2016-2017 Season**: December 4, 2016-April 8, 2017 **2017-2018 Season:** November 19, 2017-March 31, 2018 **2018-2019 Season:** December 2, 2018-April 13, 2019
Sepsis Diagnosis	One of the following codes in one of the listed diagnosis settings. **Diagnosis Code:** A41.89, A41.9, R65.20, R65.21 (ICD-10-CM) **Diagnosis Setting:** Encounter Diagnosis, Billing Diagnosis, Problem List **Start Date**: Diagnosis noted date or encounter start date
Septic Shock Diagnosis	The following code in one of the listed diagnosis settings. **Diagnosis Code:** R65.21 (ICD-10-CM) **Diagnosis Setting:** Encounter Diagnosis, Billing Diagnosis, Problem List **Start Date**: Diagnosis noted date or encounter start date

References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 February 23; 315(8): 801–810.
2. Zhou F, Yu T, Du R, et al. Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study. Lancet 2020;395:1054-62.
3. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382: 1708-20.
4. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and Viral Sepsis: Observations and Hypotheses. Lancet 2020;395:1517-20.
5. Liu D, Wang Q, Zhang H, et al. Viral Sepsis is a Complication in Patients With Novel Corona Virus Disease (COVID-19). Medicine in Drug Discovery 2020;8:100057.
6. Lin G, McGinley JP, Drysdale SB, et al. Epidemiology and Immune Pathogenesis of Viral Sepsis. Front Immunol. 2018 Sep 27;9:2147.
7. https://gis.cdc.gov/grasp/fluview/fluportaldashboard.html