



ORIGINAL RESEARCH

Death among patients hospitalized with symptomatic COVID-19: Implications for high-risk patients

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Abstract

Background: We aimed to examine the role played by the COVID-19 infection in patients' death and to determine the proportion of patients for whom it was a major contributor to death.

Methods: We included patients ≥ 50 years old who were hospitalized with COVID-19 infection and died between March 1, 2020 and September 30, 2020 in a tertiary medical center. We considered COVID-19 infection to be a major cause for death if the patient had well-controlled medical conditions and death was improbable without coronavirus infection, and a minor cause for death if the patient had serious illnesses and had an indication for palliative care.

Results: Among 243 patients, median age was 80 (interquartile intervals: 72–86) and 40% were female. One in two had moderate or severe frailty and 41% had dementia. Nearly 60% of the patients were classified as having advanced, serious illnesses present prior to the hospitalization, with death being expected within 12 months, and among this group 39% were full code at admission. In the remaining 40% of patients, deaths were classified as unexpected based on patients' prior conditions, suggesting that COVID-19 infection complications were the primary contributor to death.

Conclusions: For slightly less than half (40%) of patients who died of complications of COVID-19, death was an unexpected event. Among the 60% of patients for whom death was not a surprise, our findings identify opportunities to improve end-of-life discussions and implement shared decision-making in high-risk patients early on or prior to hospitalization.

BACKGROUND

As of October 2021, more than 660,000 people in the United States have died from complications related to COVID-19.¹ In one meta-analysis, global mortality for hospitalized patients was estimated at 17% in patients not admitted to the intensive care unit and 40% in studies of critically ill patients.² Factors associated with mortality

include older age, chronic medical conditions (e.g., diabetes mellitus, chronic lung diseases, obesity or hypertension),³ and frailty.⁴ Although it is likely that many patients who die with COVID-19 were low-risk prior to contracting the illness, the number that come from lower risk groups is unknown. In fact, some lay outlets and even scientific papers have argued that almost no low-risk patients die of COVID.^{5,6}

We sought to determine whether COVID-19 infection was a major (i.e., complications from infection were the primary contributor to catastrophic/sudden death) or minor (i.e., the patient had a serious illness at the time of admission and was likely to die within the next 12 months regardless of the presence of infection) contributor to in-hospital mortality. In addition, we used the "surprise question response" ("Would you expect that this patient will die in the next 12 months?") to better describe patient characteristics across expected mortality groups.

METHODS

Study design, setting, and patients

We conducted a retrospective cross-sectional study among patients 50 years or older who had a primary diagnosis of symptomatic COVID-19 infection and died between March 1, 2020 and September 30, 2020 in a tertiary medical center. We included patients older than 50 years because those younger than 50 are usually treated more aggressively and are more likely to be in the "low-risk of death" group. In addition, frailty is associated with high risk of adverse outcomes, and the prevalence of frailty is low for patients aged <50 years.^{7,8} The study was approved by the Baystate Medical Center Institutional Review Board with a waiver of informed consent.

Data collection

Using administrative data and detailed medical record review, a group of medical residents and one attending hospital medicine physician used a standard operating procedure to collect demographics, comorbid conditions, number of hospitalizations in the prior year, frailty, code status at admission and whether delirium was present during hospitalization. We created a standardized abstraction form and an abstraction manual which outlined the rules for data abstraction and operational definition of the terms used. The principal investigator engaged in regular monitoring of the data abstraction and regularly reviewed one out of 10 charts abstracted. We discussed disagreements to the frailty assessment and the response to the surprise questions and made changes as necessary.

Comorbid illnesses

The following medical conditions were recorded: heart failure (HF) with ejection fraction (EF) \leq 30% (as this subpopulation of patients with HF is at highest risk of death),^{9,10} severe aortic stenosis, COPD, or interstitial lung disease on home oxygen, aspiration pneumonia in the prior year, metastatic cancer, non-metastatic cancer with complications requiring hospitalization, cerebrovascular disease with

residual deficits, dementia, failure to thrive, AIDS with complications, decompensated liver failure, end-stage renal disease on dialysis, prior cardiac arrest, admission to the intensive care unit or intubation in the prior year, presence of tracheostomy or feeding tube, admission from nursing home or long-term care facility, palliative care consult or hospice enrollment in the prior year. Finally, we determined if the patient received cardiorespiratory resuscitation during the hospitalization.

Code status

We reviewed progress and palliative care notes and orders to determine whether patients were transitioned to "Do Not Resuscitate" or "Comfort Care" during the hospitalization.

Frailty

Using a combination of the admission note, physical therapy notes, and nursing assessment notes, we calculated the Clinical Frailty Scale (CFS) score.¹¹ CFS ranges from 1 (not frail) to 9 (terminally ill) with frail patients defined as those with a frailty score \geq 4 and scores 6 or higher representing moderate to severe frailty. Two prior studies have shown that CFS scores can be obtained using medical chart review and can be reliably completed by clinicians and research staff.^{12,13}

Definition of serious or advanced medical illness and determination of mortality risk

Serious or advanced illness prior to admission was defined as medical diseases or processes that are either life-threatening, life-limiting, or associated with long-term morbidity, mortality, and impairments of quality of life. We used all the following tools to classify patients as having serious illnesses prior to admission: (1) the Consensus Report from the Center to Advance Palliative Care¹⁴ for identifying patients in need of a palliative care assessment in the hospital setting (define serious illness as any disease/disorder/condition that is known to be life-limiting; e.g., dementia, COPD, chronic renal failure, metastatic cancer, cirrhosis, advanced CHD); (2) the Gold Standard Framework Prognostic indicator guidance by UK General Medical Council^{15,16} for patients approaching end of life, defined as those who are likely to die within the next 12 months (includes general indicators of decline such as activities of daily living [ADLs], increasing need or choice for no further active care and specific clinical indicators related to certain conditions including frailty); and (3) Mortensen et al. classification schema for major or minor role of pneumonia in patients death.¹⁷ We did not classify patients using each of these tools but encouraged extractors to use these various tools and scales along with the frailty assessment to help answer the "surprise" question.

The surprise question

The “surprise question” assesses the patients’ likelihood of death in the upcoming year. The original question was formulated as: “Is this person sick enough that it would be no surprise for the person to die within the next 6 months or a year?” We implemented a slightly modified version of the “surprise question” and encouraged extractors to consider objective variables prior to answering it.^{18,19} After reviewing the patient chart and collecting the above information about their prior conditions, the chart abstractor would consider the methodologies for classifying risk described above. By considering the included variables for each of the above classifications, we felt that answering a question about high versus low risk for death would be less subjective. Our version of the “surprise question” was actually three questions: (1) “Would you have been surprised if this patient died within the next 12 months if it was not for the COVID-19 hospitalization?”; (2) “Were you surprised that the patient died during this admission based on the severity of COVID-19 infection and their prior condition?”; (3) “Were you surprised that the patient died during this admission based on the course of the disease (something that was not supposed to happen, but it did).” With the first question, we wanted to understand if the patient condition prior to the hospitalization could be categorized as terminal/incurable/progressive; the answer to this question was based on a range of clinical information, including prior functionality, comorbidity, and prior health care utilization that gave a whole picture of their condition¹² prior to hospitalization. Those who were not included in this category were considered to have had a sudden/catastrophic death related to COVID infection or its complications. With the second question, we included the severity of the COVID disease presentation to the prior patient condition. The third question aimed to uncover sudden, unexpected events or complications in the disease course or potential treatment errors. To standardize data collection around frailty and the surprise question, we piloted and modified the chart abstraction form until we achieved similarity in responses for the CFS categories classification and the three surprise questions.

Outcome and analysis

We considered that COVID-19 infection was a major contributor to death (catastrophic/unexpected death) if the patient had stable medical conditions and death was a “surprise” (answer Yes to question 1). We considered COVID-19 to be a minor contributor to patient death if the patient had advanced life-threatening illnesses and COVID infection was an additional stressor on the final pathway to death (answer No to question 1). Descriptive statistics were calculated across all patients, as well as by surprise question (indicating that COVID-19 was a major vs minor contributor to death). We calculated medians and interquartile intervals (IQI: 25th to 75th percentile) for continuous variables and estimates of prevalence (frequencies and percentages) for categorical variables. As an exploratory analysis, we conducted comparisons of characteristics

across categories where COVID was determined to be a major (unexpected/sudden) or minor (other advanced illnesses) cause of death. We used Wilcoxon rank-sum test for comparison of continuous variables and Fisher exact test for categorical variables. In keeping with an exploratory analysis, we used a *p* value threshold of 0.10 as suggestive of a possible association. Statistical analysis was conducted using Stata MP (v17.0) StataCorp, LP.

RESULTS

Among the 1101 patients hospitalized with COVID-19 infection during the study period, median age was 70 (IQI: 57–82), 52% were female and 38% were non-White; 22% died, 34% were discharged home, and 23% to a skilled nursing home.

Among the 243 patients who died, the median age was 80 (IQI: 72–86) and 40% were female (Table 1). Over 50% had one or more hospitalizations in the prior year and nearly 50% had moderate to severe frailty (score 6 or higher). Approximately 41% of the patients had a diagnosis of dementia. More than half were full code at admission and 47% were admitted from a skilled nursing facility or long-term care facility. During hospitalization 8% of the patients had a cardiac resuscitation event (code blue) and 85% were made comfort care at some point during the admission. Median length of stay was 6 days (IQR: 3–12).

Nearly 60% (145/243) of the patients were classified as having an advanced, serious illnesses present prior to the hospitalization with death being expected within 12 months. The remaining 40% (98/243) deaths were classified as a “surprise,” suggesting that COVID-19 or its complications were the major contributors to death. When both the severity of the presentation and the prior conditions were considered (Question 2), only 15% of deaths were “surprising.” Finally, when considering unexpected events or complications during the hospital course (Question 3), the proportion of deaths that were “surprising” decreased to 8%.

Characteristics of those with COVID-19 infection by surprise question responses

When we compared patients who died for whom the death was not unexpected (surprise question = No) with those for whom the death was rather unexpected (surprise question = Yes) we found that the first group was older (median age 82 vs. 76), were more likely to have moderate to severe frailty (85% vs. 15%) and to have had multiple admissions in the prior year (35% vs. 18%). There was a striking difference between the code status at admission with a larger proportion being DNR/DNI among those for whom death was expected within 1 year (61% vs. 21%). These patients were also more likely to have advanced medical conditions, especially dementia, be on home oxygen, be admitted from a nursing home, and have delirium at admission or during hospitalization. Just over 90% of these patients were made comfort care prior to death compared with 77% of those

TABLE 1 Patient characteristics overall and by response to the surprise question

	Overall (N = 243)	Surprise question ^a		p Value ^b
		No 145 (59.7%)	Yes 98 (40.3%)	
Age: median (IQR)	80.0 (72.0, 86.0)	82.0 (75.0, 89.0)	76.0 (67.0, 82.0)	<0.001
Female sex	98 (40.3%)	59 (40.7%)	39 (39.8%)	0.895
Frailty score ≥ 6	121 (49.8%)	103 (85.1%)	18 (14.9%)	<0.001
Code status on admission				<0.001
Full	133 (54.7%)	56 (38.6%)	77 (78.6%)	
DNR	100 (41.2%)	82 (56.6%)	18 (18.4%)	
DNI	10 (4.1%)	7 (4.8%)	3 (3.1%)	
Comorbidities				
Advanced CHF with EF < 35%	21 (8.6%)	14 (9.7%)	7 (7.1%)	0.643
Severe aortic stenosis or other valvular diseases	20 (8.2%)	13 (9.0%)	7 (7.1%)	0.813
On home oxygen	17 (7.0%)	15 (10.3%)	2 (2.0%)	0.018
Non-metastatic cancer with complications requiring hospitalization	17 (7.0%)	12 (8.3%)	5 (5.1%)	0.445
Metastatic cancer	5 (2.1%)	3 (2.1%)	2 (2.0%)	1.000
Cerebrovascular accident with deficits	35 (14.4%)	28 (19.3%)	7 (7.1%)	0.009
AIDS with complications	2 (0.8%)	1 (0.7%)	1 (1.0%)	1.000
Decompensated liver disease	8 (3.3%)	7 (4.8%)	1 (1.0%)	0.148
Chronic kidney disease stage IV or V	26 (10.7%)	20 (13.8%)	6 (6.1%)	0.089
History of cardiac arrest	5 (2.1%)	2 (1.4%)	3 (3.1%)	0.395
COPD/asthma with prior intubation	13 (5.3%)	10 (6.9%)	3 (3.1%)	0.252
Dementia	99 (40.7%)	83 (57.2%)	16 (16.3%)	<0.001
>2 severe comorbidities other than those listed	144 (59.3%)	96 (66.2%)	48 (49.0%)	0.008
Tracheostomy	2 (0.8%)	1 (0.7%)	1 (1.0%)	1.000
Feeding tube	5 (2.1%)	3 (2.1%)	2 (2.0%)	1.000
Admission from skilled nursing facility	104 (42.8%)	86 (59.3%)	18 (18.4%)	<0.001
Admission from long-term acute care hospital	11 (4.5%)	10 (6.9%)	1 (1.0%)	0.054
Prior healthcare utilization				
# of hospitalizations in prior 12 months: median (IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	<0.001
No admissions	114 (46.9%)	50 (34.5%)	64 (65.3%)	<0.001
1 Admission	60 (24.7%)	44 (30.3%)	16 (16.3%)	
2 or more admissions	69 (28.4%)	51 (35.2%)	18 (18.4%)	
Palliative care consult in prior 12 months	10 (4.1%)	8 (5.5%)	2 (2.0%)	0.324
Current or past hospice enrollee	3 (1.2%)	2 (1.4%)	1 (1.0%)	1.000
Hospital course				
Delirium	134 (55.1%)	97 (66.9%)	37 (37.8%)	<0.001
Code blue during the hospitalization	20 (8.2%)	8 (5.5%)	12 (12.2%)	0.094
Code status changed to comfort measures only	207 (85.2%)	132 (91.0%)	75 (76.5%)	0.003
Ever placed on mechanical ventilation	78 (32.1%)	25 (17.3%)	53 (54.1%)	<0.001
LOS: median (IQR)	6.0 (3.0, 12.0)	5.0 (3.0, 10.0)	8.0 (4.0, 15.0)	0.001

(Continued)

TABLE 1 (Continued)

	Overall (N = 243)	Surprise question ^a		p Value ^b
		No 145 (59.7%)	Yes 98 (40.3%)	
Surprised that the patient died during this admission:				
Based on the presentation to the ED? (Question 2)	37 (15.2%)	4 (2.8%)	33 (33.7%)	<0.001
Based on the hospitalization course? (Question 3)	20 (8.2%)	2 (1.4%)	18 (18.4%)	<0.001

Abbreviations: AIDS, acquired immunodeficiency syndrome; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; QI, interquartile interval (25th percentile, 75th percentile).

^aWould you have been surprised if this patient would have died within 12 months if it was not for the COVID-19 hospitalization?

^bp Values from Wilcoxon rank-sum (for continuous variables) or Fisher exact (categorical variables).

with unexpected death. The evaluators were “surprised” that patients died based on their comorbidities and severity of disease at admission in 3% of those with advanced condition versus 34% of those without, and “surprised” based on hospitalization course in 1% versus 18%. Table S1 gives summaries of patients in the high and low risk for death groups based on the response to the surprise question.

DISCUSSION

In this retrospective study of 243 patients who died during a hospitalization for a COVID-19 infection, we found that almost 60% of patients had advanced, serious illnesses before their admission which could have resulted in death within one year. This result suggests that many COVID-19 related deaths occurred in patients with debilitating medical illnesses and an overall high risk of death. As expected, those for whom COVID-19 infection was considered a minor contributor (death “not a surprise”) had a high degree of frailty, with half of them being moderately or severely frail. Yet, in 40% of patients who died while infected with COVID, death was unexpected. Of patients who were not expected to die, the severity of COVID infection (measured by, among other factors, the need for critical care services) and related complications helped to explain over 80% of these deaths.

A prior study conducted in the same institution examined whether pneumonia was a major or a minor contributor to patients' death.²⁰ In this prior study, pneumonia was considered a major contributor to death in only 18% of the cases, suggesting that the vast majority of deaths due to “pneumonia” were in older, ill, or frail patients.²⁰ Comparatively, the mortality rate for the COVID-19 admissions was higher than the mortality rate for pneumonia rates (22% vs. 15%).²¹ This higher mortality rate, taken in combination with the greater number of “surprise” deaths, suggest that COVID-19 infection is more aggressive than usual community-acquired pneumonia. And, contrary to our prior work in pneumonia, COVID-19 is not a disease that kills primarily older people, frail people, or those with multiple comorbidities. Before becoming sick, the “surprise” group was highly functioning, and their medical conditions were well controlled. Our findings suggest that among those who died with severe COVID-19, nearly half died prematurely.

During the first wave of COVID-19 when hospitals were overwhelmed with patients, several strategies for risk stratification were used including age in the context of comorbidities and/or frailty. For example, the Swiss Academy of Medical Sciences suggested the use of Advance Care Planning (ACP) when managing older people leaving with frailty diagnosed with COVID-19.^{22–24} In the UK, the National Institute for Health and Care Excellence (NICE) updated its recommendations on managing critical care patients to include frailty screening for all older adults.²⁵ In our study, over half of patients were full code at the time of admission, and the proportion who were full code varied with respect to likelihood of death. Still 39% of those with serious illnesses and high risk of death in the context of COVID infection were full code at admission, many received aggressive care and 6% had a cardiac resuscitation. Hospitalization for COVID-19 could provide an opportunity for ACP with shared-decision making regarding aggressive medical care for frail older adults. Several studies have shown inconsistency between patient preference for end-of-life care and what is happening in real life.²⁶ Most patients with an advanced illness prefer to die at home, yet many of them receive aggressive interventions, and many die in the hospital.²⁷ These findings suggest significant opportunities to improve end-of-life discussions and implement shared decision making tools regarding code status or goal concordant care, particularly in high-risk patients (such as those with dementia that are dependent on surrogate decision makers) early in (or even prior to) hospitalization events, during the COVID-19 pandemic. We need to identify patients with a high likelihood of death early in the hospitalization and then initiate a goals of care discussion. During this discussion, we should focus on identifying preferences for care during the hospitalization,²⁸ and should specifically ask about end-of-life care.

Almost 40% of all deaths occurred among patients who had an advanced illness and decided to forgo aggressive treatments at the time of admission. However, even in this group, COVID-19 is rarely a “by-stander.” Rather, in the setting of the patients' other comorbidities, COVID-19 infection was the aggressive, final stressor in the pathway of illness. The exact timing of the final hospitalization and the patients' eventual death appears related to contracting COVID-19.

The prevalence of frailty in our study is similar to a meta-analysis of 15 studies (23,944 COVID patients), which found that the pooled prevalence of frailty was 51%. These patients had twice the risk of

death compared with those without frailty.^{23,24,29} As described above, in the UK, the National Institute for Health and Care Excellence (NICE) has updated its guideline on critical care on March 2020 to involve frailty screening for all older adults.^{25,30} Implementing a formal frailty assessment for patients hospitalized with COVID-19 infection will support appropriate goals of care discussion as well as frailty-attuned care.

This study has several limitations. Identifying patients with potential life-limiting or life-threatening conditions represents a broad construct that could be opened to variable interpretation, especially when the reviewers were not blinded to the outcomes. In addition, the surprise question has a relatively low specificity and sensitivity.³¹ However, we used a variety of criteria for defining serious illnesses to inform the response to the surprise question and we piloted the chart review form extensively. Second, the study was done in one institution, and practices could vary across institutions. Third, we examined only inpatient deaths; one study of more than 4000 patients with COVID-19 found that 26% of patients had died at Day 28 and an additional 5% died by Day 90,³² so our results apply only to deceased hospitalized patients. Fourth, as this sample was highly selected (e.g., infected, hospitalized, and deceased) and without a denominator (e.g., infected and hospitalized), we cannot infer causation or interpret patient factors as risk factors. Fifth, we could not classify dementia according to its severity. Lastly, our study included patients who died from March to September 2020 and in the meanwhile vaccines and other therapeutics may have changed the course of the disease.

In conclusion, more than half of patients who died of COVID-19 complications were elderly with advanced, serious illnesses, but for nearly half, death was an unexpected event. These findings suggest that prevention measures for high-risk individuals, population health measures to limit transmission among those at risk (e.g., masks, vaccines), and novel therapeutic interventions should continue to be high priorities in the fight against this deadly pandemic. Among the 60% of patients for whom death was not a surprise, our findings identify opportunities to improve end-of-life discussions and implement shared decision-making in high-risk patients early on or prior to hospitalization.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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