Post-discharge mortality among patients hospitalised with severe acute respiratory infection, Bangladesh, 2012–2019: a prospective observational study

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Summary

Background Enhancing outcomes post-hospitalisation requires an understanding of predictive factors for adverse events. This study aimed to estimate post-discharge mortality rates among patients with severe acute respiratory infection (SARI) in Bangladesh, identify associated factors, and document reported causes of death.

Methods From January 2012 to December 2019, we conducted follow-up calls to patients or their families 30 days after discharge to assess the status of patients with SARI. Proportions of deaths within 30 days of discharge were estimated, and a comparative analysis of demographics, clinical characteristics, and influenza illness between decedents and survivors was performed using multivariable Cox regression models.

Findings Among 23,360 patients with SARI (median age: 20 years, IQR: 1.5–48, 65% male), 351 (1.5%) died during hospitalisation. Of 23,009 patients alive at discharge, 20,044 (87%) were followed, with 633 (3.2%) deaths within 30 days of discharge. In children (<18 years), difficulty breathing (adjusted hazard ratio [aHR] 1.8; 95% CI 1.1–3.0), longer hospital stay (aHR 1.1; 95% CI 1.1–1.1), and heart diseases (aHR 8.5; 95% CI 3.2–23.1) were associated with higher post-discharge death risk. Among adults (≥18 years), difficulty breathing (aHR 2.3; 95% CI 1.7–3.0), chronic obstructive pulmonary disease (aHR 1.7; 95% CI 1.4–2.2), and intensive care unit admission (aHR 5.2; 95% CI 1.9–14.0) were linked to elevated post-discharge death risk. Influenza virus was detected in 13% (46/351) of in-hospital SARI deaths and 10% (65/633) of post-discharge SARI deaths.

Interpretation Nearly one in twenty patients with SARI died during hospitalisation or within 1 month of discharge, with two-thirds of deaths occurring post-discharge. Seasonal influenza vaccination is recommended to mitigate influenza-associated mortality. To enhance post-discharge outcomes, hospitals should consider developing safe-discharge algorithms, reinforcing post-discharge care plans, and establishing outpatient monitoring for recently discharged patients.

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Keywords: Influenza; Post-discharge mortality; Severe acute respiratory infection; Surveillance; Bangladesh

Introduction

While in-hospital influenza deaths are readily quantifiable through sentinel surveillance, there is a paucity of data on post-discharge survival, strategies for improvement, and the potential implications for our comprehensive understanding of global acute respiratory infection (ARI) mortality. Influenza, a vaccine-preventable cause of severe acute respiratory infection (SARI), offers an avenue for understanding the added benefits of vaccination programs.

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Research in context

Evidence before this study

While sentinel surveillance provides valuable insights into in-hospital mortality among patients with severe acute respiratory infection (SARI), there exists a notable dearth of information regarding post-discharge SARI mortality and its prevention. This knowledge gap is particularly pronounced in countries such as Bangladesh, where no comprehensive analyses or long-term studies have been undertaken. Understanding the risk factors associated with post-discharge mortality is crucial for the development of effective interventions aimed at reducing the burden of SARI mortality. Therefore, urgent research is needed to address this critical gap in knowledge.

Added value of this study

In this 8-year prospective study, we aimed to estimate the proportion of SARI-related deaths occurring within 30 days of discharge. We conducted a comparative analysis of demographics, clinical characteristics, and influenza illness between decedents and survivors. Approximately 5% of patients with SARI succumbed to the illness, with two-thirds of these deaths occurring within 30 days post-discharge. This highlights the potential oversight of deaths happening after discharge in understanding the true burden of SARI mortality in Bangladesh. Our findings revealed higher post-discharge mortality rates in infants and older adults, with most deaths occurring within the first week post-discharge. Factors such as comorbid conditions, intensive care unit (ICU) admission, and extended hospital stays were associated with post-discharge mortality. Additionally, our study indicated that influenza virus infections may contribute significantly (10%) to post-discharge SARI deaths.

Implications of all the available evidence

A comprehensive understanding of factors linked to post-discharge SARI deaths, particularly those associated with influenza, holds implications for policy decisions on prevention and control measures, including vaccination programs. The study's outcomes provide valuable insights for health authorities to formulate interventions aimed at enhancing patient outcomes post-discharge and preventing avoidable deaths. This long-term study addresses a crucial knowledge gap in Bangladesh, serving as a foundation for future research and interventions to mitigate the burden of SARI mortality.

SARI stands out as a leading global cause of morbidity and mortality, particularly affecting children under 5 years old.[1] More than 90% of SARI-related deaths occur in developing countries, including Bangladesh,[1] where influenza-associated SARI is prevalent and could play a significant role in mortality.[2] Globally, influenza is estimated to result in 3–5 million severe illnesses and 291,000–646,000 influenza-associated respiratory deaths.[3]

Death post-hospital discharge among patients with SARI remains insufficiently characterised, especially in low-income and middle-income countries (LMICs) such as Bangladesh. Many SARI surveillance systems, including Bangladesh's hospital-based influenza surveillance (HBIS) system, primarily capture in-hospital deaths.[4] However, a systematic review focusing on paediatric post-discharge mortality in LMICs revealed higher proportions of post-discharge deaths compared to in-hospital deaths, signalling a potential gap in comprehending the causes and burden of SARI mortality.[5]

A nuanced understanding of SARI mortality, encompassing both in-hospital and post-discharge scenarios, can significantly influence policy decisions regarding prevention and control measures, notably vaccination programs. Our study aimed to ascertain the proportion of individuals hospitalised with SARI who succumbed within 30 days of discharge. We sought to identify associated risk factors, shedding light on reported causes of death by leveraging the HBIS system in Bangladesh coupled with patient follow-up.

Methods

Study settings and study population

In this prospective observational study, we assessed the post-discharge deaths among patients with SARI within the HBIS system in Bangladesh from January 2012 to December 2019. The surveillance initiative was jointly implemented by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), and the Institute of Epidemiology, Disease Control, and Research (IEDCR) of the Government of Bangladesh (GoB). Respiratory infection surveillance covered up to 14 hospitals (annual range 7–14) throughout Bangladesh from 2012 to 2019 (Fig. 1). Surveillance initially focused on general medicine and paediatric wards until January 2018 when coverage expanded to include intensive care units (ICUs) and coronary care units. Surveillance in ICUs was discontinued in January 2019 due to a low number of SARI admissions. Detailed surveillance methods have been previously documented.[6]

Case identification, data and sample collection, and laboratory analysis

Surveillance physicians diligently monitored admissions, identifying individuals meeting the SARI case definition based on the WHO criteria, which evolved during the study period. From January 2012 to June 2016, SARI for individuals aged ≥5 years was defined as acute respiratory illness with fever (or measured fever ≥38 °C) and cough or sore throat, with onset within the previous 7 days, necessitating hospitalisation.[7] For those

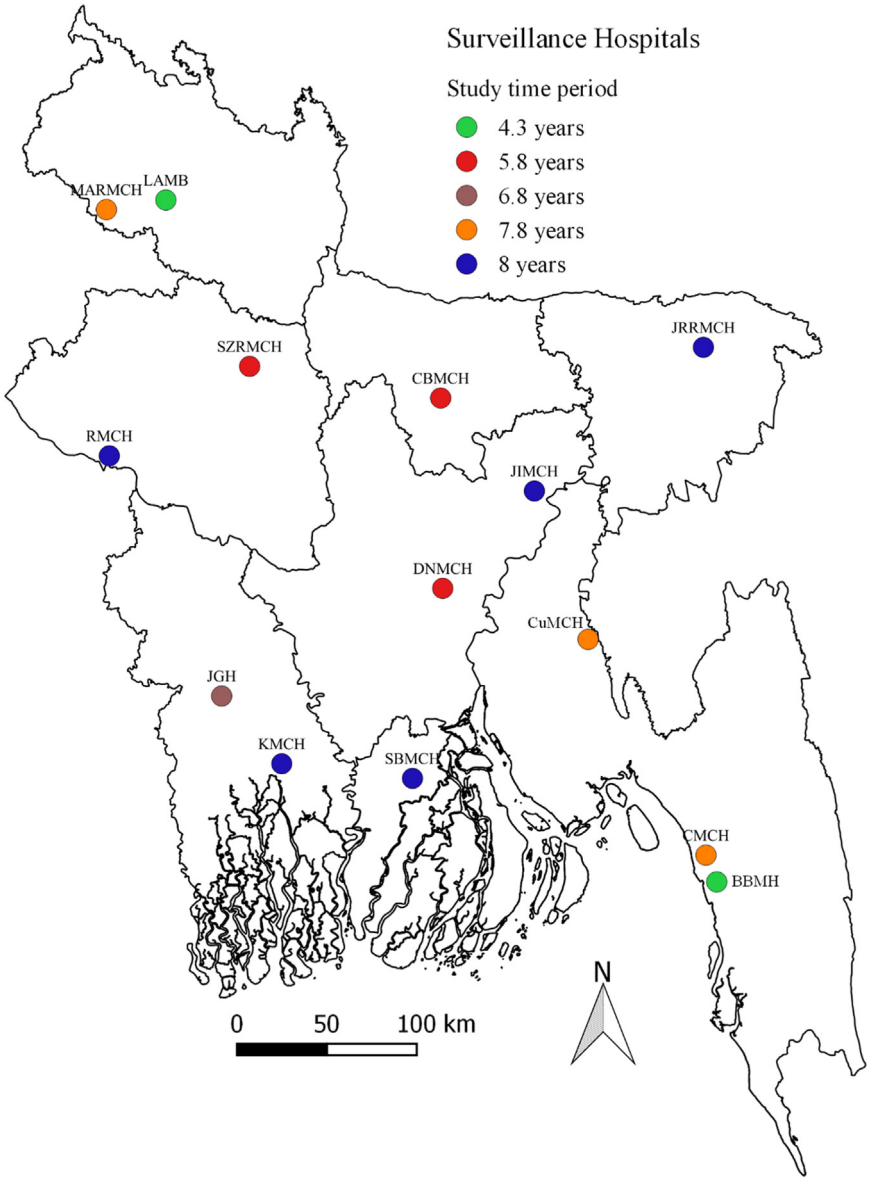

Fig. 1: Map of Bangladesh indicating the 14 surveillance hospitals with the study time-period for each. Hospital distribution: January 2012–March 2014 (12 sites), April 2014–April 2016 (14 sites), May 2016–September 2017 (12 sites), October 2017–December 2017 (7 sites), January 2018–November 2018 (8 sites), December 2018–December 2019 (9 sites). DNMCH: Dhaka National Medical Collage Hospital, CBMCH: Community Based Medical Collage Hospital, JIMCH: Jahurul Islam Medical Collage Hospital, RMCH: Rajshahi Medical Collage Hospital, SZRMCH: Shaheed Ziaur Rahman Medical College Hospital, LAMB: LAMB Hospital, BBMH: Bangabandhu Memorial Hospital, CuMCH: Cumilla Medical College Hospital, KMCH: Khulna Medical College Hospital, JGH: Jashore 250 bed General Hospital, JRRMCH: Jalalabad Ragib-Rabeya Medical College and Hospital, SBMCH: Sher-E-Bangla Medical College Hospital, CMCH: Chattogram Medical College Hospital, MARMCH: M Abdur Rahim Medical College Hospital.

<5 years during the same period, SARI constituted severe pneumonia or a history of cough or difficulty breathing, accompanied by at least one danger sign: chest indrawing, stridor in a calm child, history of convulsions, inability to drink, lethargy, unconsciousness, or intractable vomiting within 7 days of hospitalisation.[8] Since July 2016, SARI for all ages has been classified as an ARI with fever (or measured fever ≥38 °C) and cough, with onset within 10 days of hospitalisation.[9]

Upon identifying patients with SARI and securing written informed consent, surveillance physicians enrolled participants, collecting data on demographics, smoking history, comorbidities, clinical signs and

symptoms, treatment, and outcome status at initial hospital discharge. Respiratory swabs (nasopharyngeal and oropharyngeal) were collected, with all samples tested for influenza viruses using real-time reverse transcription polymerase chain reaction (rRT-PCR) during the influenza season (usually during April–September). From October to March, every second sample from patients aged ≥5 years and two randomly selected samples from children aged <5 years per surveillance hospital each week were subjected to influenza virus testing using rRT-PCR. Subtyping was done for the samples positive for influenza A. The HBIS surveillance protocol received approval from the institutional review board of icddr,b (protocol #2007-002), with reliance approval from the U.S. Centers for Disease Control and Prevention.

Hospital discharge

We gathered information on hospital discharge for each patient with SARI upon leaving the hospital. Discharge details were categorised as follows: (i) patients with a medical record indicating full recovery, (ii) patients or their families requesting early discharge, (iii) patients discharged early based on a physician's advice, and iv) patients referred to a specialised hospital. Premature discharge was defined when the patient or their family requested early discharge, and the early discharge was advised by a physician.

Post-discharge follow-up

For discharged patients with SARI, we conducted a follow-up survey after 30 days (a timeframe utilised in several previous studies) to ascertain the outcome of the SARI episode. Field staff contacted the patient or a family member by telephone to inquire about the patient's status. If the patient was unreachable, they received up to three additional telephone calls. If the respondent was ≥18 years and agreed to participate, or if the patient was <18 and provided assent and their parent or guardian consented, the follow-up interview was initiated with the patient, parent, or guardian. We collected information about outcomes, additional healthcare-seeking behaviours, or hospital re-admission for the episode. In the case of patient demise, family members or caregivers were interviewed using a structured questionnaire to gather information on the date, place of death, and self-reported causes of death. Deaths due to road traffic accidents, poisoning, homicide, drowning, and other accidents were excluded from the study.

Statistical analysis

We analysed categorical variables using frequency and percentages, comparing the percentages using two-sample z-tests. Numerical variables were analysed using the median and IQR, and group comparisons were made using nonparametric equality-of-medians tests. We calculated the proportion of patients with SARI who died in-hospital and compared this to the proportion who died within 30 days after discharge, excluding accidental deaths. We quantified the case fatality proportion (CFP) of patients with SARI at discharge (in-hospital deaths or patients with SARI) and quantified the CFP of patients with SARI who died within 30 days after discharge (post-discharge deaths or cases who were discharged). Kaplan–Meier curves for 30-day post-discharge mortality were generated.

Among children aged <18 years, potential risk factors for post-discharge deaths, such as age, sex, difficulty breathing reported on admission, duration of symptoms prior to hospital admission, length of hospital stay, ICU admission, and comorbidities (asthma and heart diseases) reported during hospitalisation, as well as the detection of influenza viruses, were assessed by comparing patients who died with survivors at 30 days post-discharge. Specific risk factors for post-discharge deaths for younger children, such as nutritional status, anthropometric measurements, social status of family members, and smoking history of children aged <18 years or their parents, were not collected. ICU admission data for children aged <18 years were excluded from multivariate analysis due to insufficient observation.

Among adults aged ≥18 years, potential risk factors for post-discharge deaths, including age, sex, difficulty breathing reported on admission, duration of symptoms prior to hospital admission, length of hospital stay, ICU admission, smoking history, comorbidities (asthma, chronic obstructive pulmonary disease [COPD], diabetes, hypertension, and heart diseases) reported during hospitalisation, and the detection of influenza viruses, were assessed by comparing patients who died with survivors at 30 days post-discharge. Patients enrolled after May 2013, when self-reported comorbidity information was included, were considered in this analysis.

Based on previous work[10] and our experience, we classified variables into hierarchical levels for children aged <18 years (Table S1A) and adults aged ≥18 years (Table S1B). The hierarchical levels included sex and age as the most distal level variables. For children, the second level included comorbidities (i.e., asthma and heart diseases) and the detection of influenza RNA through rt-PCR. The third level included difficulty breathing, length of hospital stay, and duration of symptoms prior to hospital admission as the most proximal level variables. For adults, the second level included smoking history. The third level included comorbidities (i.e., asthma, COPD, hypertension, diabetes, and heart diseases) and the detection of influenza RNA through rt-PCR. The fourth level included difficulty breathing, length of hospital stay, duration of symptoms prior to hospital admission, and ICU admission as the most proximal level variables. Hazard ratios with 95%

confidence intervals (CIs) were estimated using a multivariable Cox regression model.

Initially, all explanatory variables (potential risk factors) of each level were entered into their respective models. Initial risk factors at a 5% level of significance were identified for each level. Selected initial risk factors were jointly included in the model for each level, controlling for all variables retained in previous levels at a 10% level of significance. Variables were progressively excluded at each level, retaining only those statistically significant at a 5% level of significance. In the final model, hazard ratios were simultaneously adjusted for variables in the same hierarchical level and those retained in previous levels (Table S1). All analyses were conducted using Stata 13.0 software (StataCorp. 2013. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

Role of the funding source

This research study was funded by Centers for Disease Control and Prevention (CDC). CDC staff also assisted with refining study design, interpretation of data, and editing of the manuscripts.

Results

Study patient characteristics and post-discharge follow-up

From January 2012 to December 2019, we identified 23,360 patients with SARI. The median age of patients with SARI was 20 years (IQR: 1.5–48.0, range: 0.1–105), with 65% being male. Among patients with SARI, 1.5% (351) died during hospital admission. Of the 23,009 patients with SARI alive at discharge, 2965 were lost to follow-up. Among the 20,044 (87%) patients who completed the survey, 3.2% (633/20,044) died within 30 days of hospital discharge. During our study period, 4.8% (984/20,395) of patients with SARI died: 36% (351/984) died in-hospital, and 64% (633/984) died within 30 days of discharge (Table 1, Fig. 2).

Among the 633 post-discharge deaths, 233 (37%) had a medical record of being fully recovered at discharge, 304 (48%) had a medical record of being partially recovered or prematurely discharged, and 96 (15%) had a referral to a specialised hospital. Of the 304 prematurely discharged patients, 175 (58%) patients or their family requested discharge, and 129 (42%) were discharged on the advice of a physician (Fig. 2, Table S2). Among post-discharge deaths, 409 (65%) occurred within the first 2 weeks of discharge. Of these deaths, 128/409 (31%) had a discharge note stating the patient was fully recovered at the time of discharge. The remaining 281/409 post-discharge deaths had notes stating that discharge was requested by the patient or their family (124, 30%), on the advice of a physician (80, 20%), or with a referral to a specialised hospital (77, 19%).

Children aged <1 year hospitalised with SARI (3% [122/4128]) were more likely to die within 30 days following discharge compared to children aged 2–5 years (1% [19/1635]; $p < 0.001$). Among children aged <1 year who died within 30 days of discharge, 57 (47%) had a medical record note of being fully recovered at discharge, 26 (21%) had notes documenting a request for discharge by the patient or their family, 22 (18%) on the advice of a physician, and 17 (14%) with a referral to a specialised hospital. Adults aged ≥65 years (11% [224/2133]) were more likely to die within 30 days post-discharge compared to those aged 6–65 years (2% [268/12,148]; $p < 0.001$). Among adults aged ≥65 years who died within 30 days post-discharge, 90 (40%) had notes documenting a request for discharge by the patient or their family at discharge, 75 (33%) had a medical record note of being fully recovered, 33 (15%) on the advice of a physician, and 26 (12%) with a referral to specialised hospitals.

Characteristics of patients who died after discharge, and time and place of death

Among the 633 patients with SARI who died following discharge, the median time between symptom onset and admission was 3 days (IQR: 2–5 days). The median length of hospital stay for these patients was 4 days (IQR: 2–6 days). The median time between symptom onset and death was 17 days (IQR: 10–28 days) (Table S3).

Sixty-eight percent (428/633) of post-discharge deaths occurred at the patient's home, and 32% (205/633) occurred during a hospital readmission (reasons not documented). Among patients who died in the 30-day post-discharge period, 50% (317/633) of deaths occurred in the first 7 days (14% [87/633] within 24 h), 15% (92/633) within 8–14 days, 13% (83/633) within 15–21 days, and 22% (142/633) within 22–30 days following discharge (Fig. 3, Table S2).

Among those who died during post-discharge with a medical record note of being fully recovered at initial discharge, 55% (128/233) died during the first 2 weeks of discharge, and 45% (105/233) died after 2 weeks of discharge. Among those who died during the post-discharge period identified as premature discharge (having medical record notes documenting a request for discharge by the patient/their family or on the advice of a physician), 67% (204/304) died during the first 2 weeks of discharge, and 33% (100/304) died after 2 weeks of discharge (Table S2).

Causes of death reported by family members

Among patients with SARI who died after discharge, the most common reported causes of death included shortness of breath (36%, 230), pneumonia (14%, 89), fever (9%, 57), heart disease (9%, 57), and 4% with no cause reported (Fig. 4). Among the patients with SARI who had medical record notes of being fully recovered at discharge (233), family-reported causes of death were shortness of breath (35%, 82), pneumonia (19%, 44), fever (11%, 27), heart disease (11%, 26), stroke (4%, 10),

Characteristics	Patients enrolled N = 23,360	In-hospital deaths N = 351		Follow-up completed after discharge[b] N = 20,044	Post-discharge deaths N = 633	
		n (%)	p-value		n (%)	p-value
Demographic characteristics						
Age						
<1 year	5027	101 (2.0)	<0.001	4128	122 (3.0)	<0.001
2–5 years	1925	19 (1.0)		1635	19 (1.2)	
6–18 years	3562	5 (0.1)		3163	27 (0.9)	
19–40 years	5356	40 (0.8)		4778	49 (1.0)	
41–65 years	4919	96 (2.0)		4207	192 (4.6)	
≥65 years	2571	90 (3.5)		2133	224 (10.5)	
Median age (IQR), years	20 (1.5–48)	45 (0.5–65)	<0.001	20 (1.7–46)	55 (14–70)	<0.001
Male	15,162	238 (2)	0.251	13,008	479 (4)	<0.001
Clinical characteristics						
Runny nose	10,848	106 (1.0)	<0.001	921	196 (2.1)	
Headache	9199	66 (0.7)	<0.001	8192	174 (2.1)	<0.001
Sore throat	2816	20 (0.7)	<0.001	2474	47 (1.9)	<0.001
Chest indrawing[c]	5371	108 (2.0)	<0.001	4363	124 (2.8)	<0.001
Difficulty breathing reported on admission	14,346	310 (2.2)	<0.001	11,981	536 (4.5)	<0.001
Body ache	7575	65 (0.9)	<0.001	6675	181 (2.7)	<0.001
Duration of symptoms prior to admission in days; Median (IQR)	3 (2–4)	3 (2–4)	0.7956	3 (2–4)	3 (2–5)	0.0023
Length of hospital stay in days; Median (IQR)	4 (2–5)	2 (1–5)	<0.001	3 (2–5)	4 (2–6)	<0.001
Comorbidity						
≥1 co-morbid condition (self-reported)[d] (n = 20,525)	4441	120 (2.7)	<0.001	3815	263 (6.9)	<0.001
COPD	1299	42 (3.2)	<0.001	1115	131 (11.8)	<0.001
Asthma	1789	31 (1.7)	0.377	1517	66 (4.4)	0.009
Diabetes	733	27 (3.7)	<0.001	645	46 (7.1)	<0.001
Heart diseases	386	17 (4.4)	<0.001	334	28 (8.4)	<0.001
Hypertension	1175	32 (2.7)	<0.001	1030	68 (6.6)	<0.001
Cancer	17	2 (12)	<0.001	15	5 (33.3)	<0.001
Liver disease	23	2 (8.7)	0.004	19	0 (0)	–
Kidney disease	68	3 (4.4)	0.046	57	8 (14.0)	<0.001
Treatment received						
Antibiotic[e]	17,155	254 (1.5)	0.785	14,770	490 (3.3)	0.088
Oseltamivir	6	0 (0)	0.762	6	1 (16.7)	0.058
Oxygen	5095	213 (4.2)	<0.001	4269	306 (7.2)	<0.001
Mechanical ventilation	25	9 (2.6)	<0.001	16	4 (25)	<0.001
ICU support (after admission in the general ward)	28	9 (3.0)	<0.001	19	5 (26.3)	<0.001
Laboratory results						
Influenza virus detected	4260	46 (1.1)	0.012	3714	65 (1.8)	<0.001
Influenza A	2839	32 (1.1)	0.773	2456	52 (2.1)	0.047
Influenza B	1414	14 (1.0)		1252	13 (1.0)	
Influenza A and B	7	0 (0)		6	0 (0)	
Subtypes of influenza A (N = 2839)						
Influenza A (H1N1)pdm09	1456	17 (1.2)	1.000	1274	29 (2.3)	0.306
Influenza A (H3N2)	1364	15 (1.1)		1163	22 (1.9)	
Influenza A (H5N1)	1	0 (0)		1	0 (0)	
Co-infected with A (H3N2) and A (H1N1)pdm09	2	0 (0)		2	0 (0)	
Influenza A (inconclusive[a])	16	0 (0)		16	1 (6.2)	

Note: interquartile range (IQR), chronic obstructive pulmonary disease (COPD), intensive care unit (ICU). [a]Inconclusive: Unable to characterise due to insufficient viral load in samples. [b]Follow-up data were collected from 20,044 patients with SARI, excluding in-hospital deaths (N = 351) and those lost to follow-up (N = 2965). [c]Data on chest indrawing were collected for the patients with SARI aged <5 years only. [d]Data collection on self-reported comorbidity was initiated in May 2013. Comorbid conditions (chronic diseases) included asthma, COPD/chronic bronchitis/emphysema, diabetes, hypertension, ischaemic heart disease, cancer, kidney disease, and liver disease. [e]Data collection on antibiotic treatment was initiated in May 2013.

Table 1: **Demographic, clinical, and laboratory characteristics of in-hospital and post-discharge death cases in selected hospitals in Bangladesh, 2012–2019.**

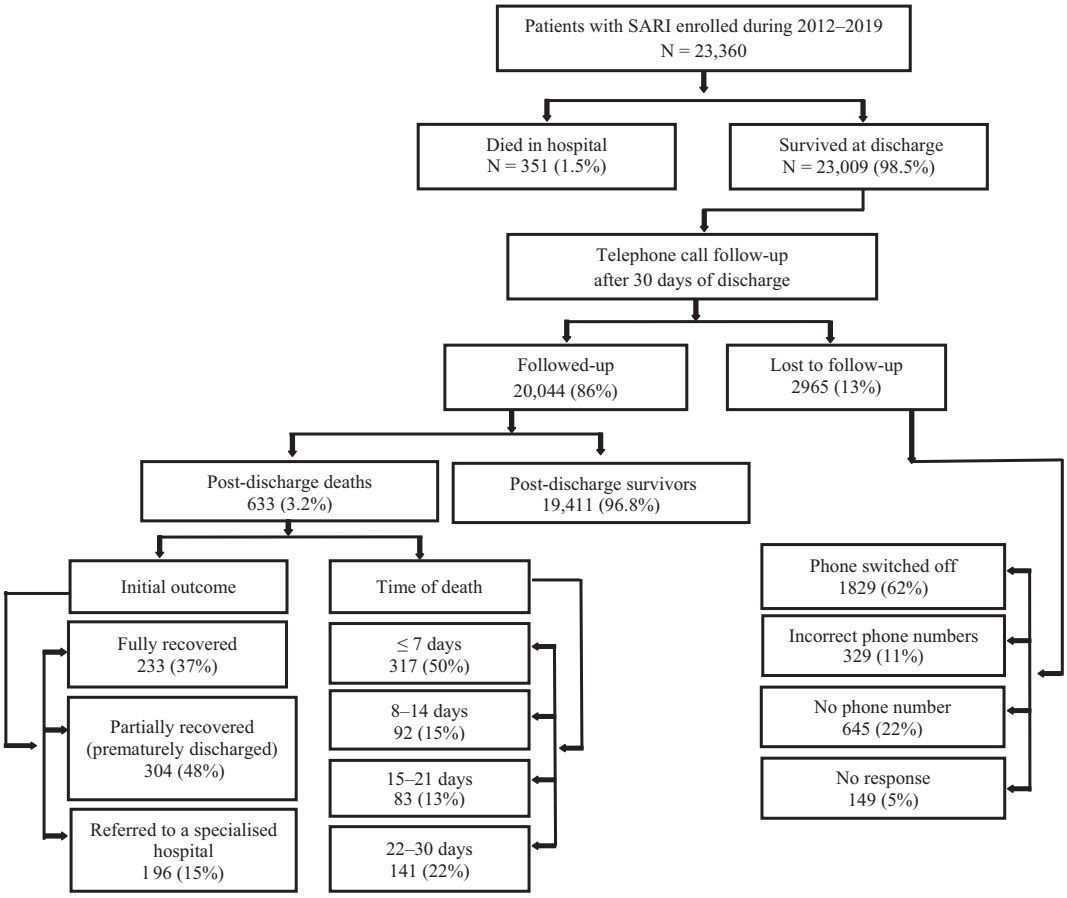

Fig. 2: Flowchart depicting the enrolment and 30-day post-discharge follow-up of patients with SARI in selected hospitals during 2012–2019, Bangladesh.

chest pain (3%, 6), asthma (2%, 4), other diseases (7%, 18), and 16 (7%) with no cause reported.

Laboratory characteristics among patients with SARI with post-discharge deaths

Among 23,360 patients with SARI, 18% (4260) were positive for influenza viruses, of which 67% (2839) were influenza A, 33% (1414) influenza B, and 0.2% (7) were co-infected with influenza A and B. Influenza virus was detected in 19% (3649) of patients with SARI who survived at discharge. About the same proportion of influenza viruses were detected among in-hospital SARI deaths (13% [46/351] vs. 10% [65/633], $p < 0.178$) compared to patients with SARI who died within 30 days following discharge (Table 1). Among the post-discharge deaths, the highest influenza positivity was observed in age groups of 6–18 years (15%, 4/27), followed by age groups of 41–65 years (13%, 24/192), age groups of 2–5 years (11%, 2/19), age groups of ≥65 years (10%, 22/224), and age groups of 19–40 years (8%, 4/49). Influenza positivity was lowest in children aged <1 year (7%, 9/122).

Of the post-discharge deaths, 48% (305/633) occurred during the influenza season (usually during April–September), and 52% (328/633) occurred during the rest of the year (October–March). Among all influenza-positive deaths, 59% (65/111) occurred during post-discharge. One in ten post-discharge deaths was positive for influenza compared with one in five post-discharge survivors (Table 1). Among patients who were influenza-positive, influenza A was the most common influenza type among in-hospital deaths, post-discharge deaths, and patients who were alive at 30 days post-discharge.

Treatment history of patients with SARI with post-discharge deaths

Of 23,360 patients with SARI, five patients (0.03%) who survived and one patient (0.004%) who died within 30 days post-discharge received oseltamivir during hospitalisation, although it was not clear how long after admission it was given. There was no statistically significant difference in antibiotic use between patients with SARI who died or survived (86% vs. 83%, $p = 0.088$) (Table 1).

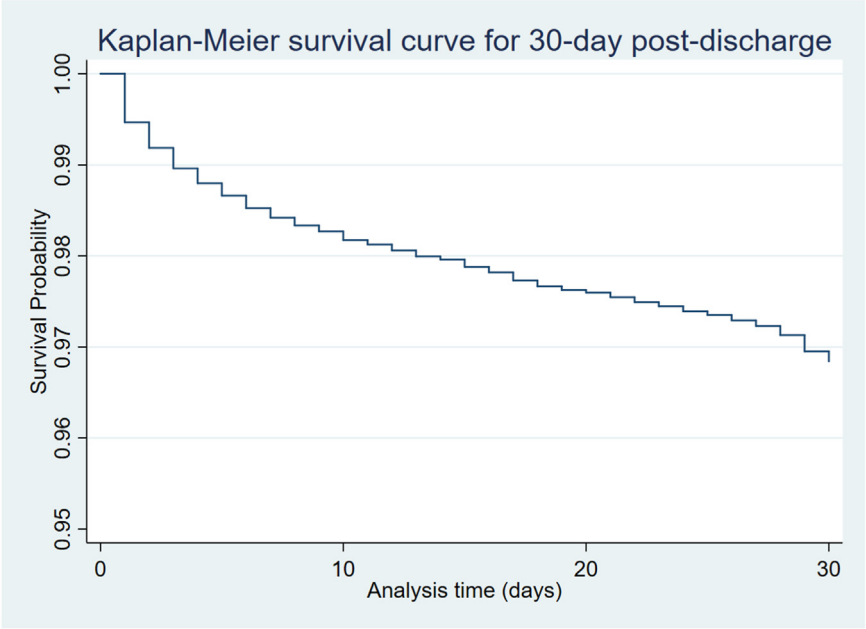

Fig. 3: Kaplan–Meier estimate illustrating 30-day post-discharge deaths (N = 633) among patients with SARI in Bangladesh during 2012–2019.

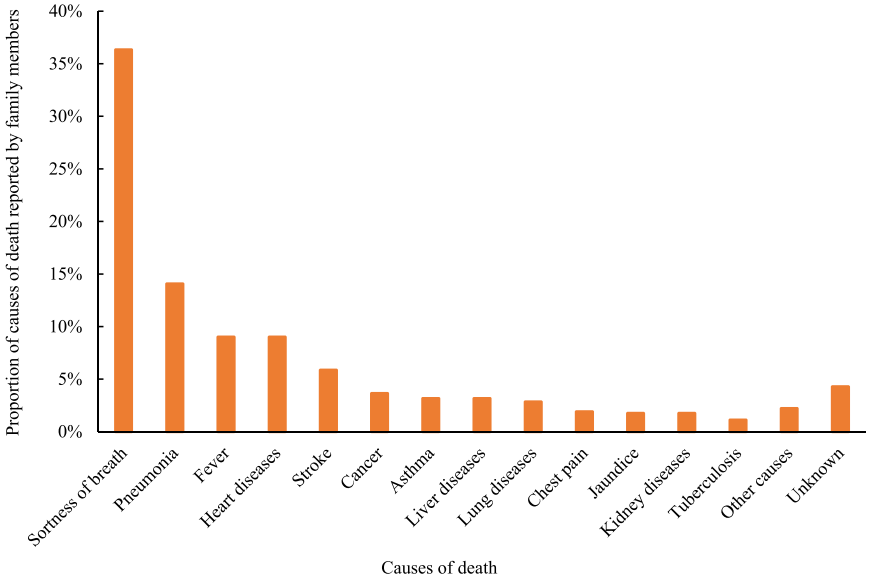

Fig. 4: Family member-reported causes for death among patients with SARI who died within 30 days of post-discharge during 2012–2019 in Bangladesh.

Factors associated with patients with SARI's post-discharge mortality

Among children aged < 18 years: After controlling for age and influenza virus detection, patients with SARI reporting heart diseases were 8.5 times more likely to die within 30 days post-discharge than patients not reporting heart diseases (CI 95%: 3.2–23.1). Controlling for age, length of hospital stay, influenza virus detection, and heart disease, difficulty breathing was 1.8 times more likely to die within 30 days post-discharge than cases not reporting difficulty breathing (CI 95%: 1.1–3.0). Additionally, the risk of post-discharge deaths

Model	Factors	aHR	95% CI	p-value
Model-1	Age in years	0.90	0.86–0.94	<0.001
	Sex (male)	0.87	0.62–1.22	0.412
Model-2	Asthma	0.66	0.21–2.08	0.482
	Heart diseases	8.70	3.21–23.55	<0.001
	Influenza virus detected	0.41	0.22–0.78	<0.001
Model-3	Duration of symptoms prior to admission in days	1.05	0.96–1.15	0.257
	Length of hospital stay in days	1.08	1.05–1.11	<0.001
	Difficulty breathing	2.82	1.83–4.34	<0.001
Model-4	Heart diseases	8.53	3.16–23.08	<0.001
	Influenza virus detected	0.53	0.27–1.01	0.053
Model-5	Length of hospital stay in days	1.09	1.06–1.12	<0.001
	Difficulty breathing	1.84	1.12–3.01	0.016

Note: adjusted hazard ratio (aHR), confidence interval (CI). In Models 1–3, we presented the direct relationship between the outcome and explanatory variables/potential predictors at each level without adjusting for variables from other levels. Model 4 incorporated heart diseases and influenza virus detected variables, along with age variables as covariates. In Model 5, the covariates included length of hospital stay in days and difficulty breathing variables, along with the covariates heart diseases, influenza virus detected, and age variables. The results for adjusted variables are detailed in Table S4. Data collection on self-reported comorbidities (e.g., asthma and heart diseases) commenced in May 2013 (N = 9055).

Table 2: **Factors associated with post-discharge deaths among children aged <18 years (N = 10,514) who were admitted to selected hospitals in Bangladesh.**

increased by 9% for each day the patient was in the hospital (1.09 [CI 95%: 1.1–1.1]) (Table 2).

Among adults aged ≥ 18 years: After controlling for age and influenza virus detection, diabetes, duration of symptoms prior to admission, length of hospital stay, ICU admission, and COPD, SARI cases reporting difficulty breathing were 2.3 times more likely to die within 30 days post-discharge than cases not reporting difficulty breathing (CI 95%: 1.7–3.0). Controlling for age, sex, smoking status, diabetes, heart diseases, hypertension, asthma, and influenza virus detection, patients with SARI reporting COPD were 1.7 times more likely to die within 30 days post-discharge than those not reporting COPD (CI 95%: 1.4–2.2). Patients with SARI admitted to the ICU had a 5.2 times higher risk of death within the 30 days following discharge than patients not admitted to the ICU (CI 95%: 1.9–14.0) (Table 3).

Discussion

The current study revealed that the proportion of SARI and SARI-influenza cases that died after discharge, excluding unrelated deaths, was equal to or greater than the proportion that died during hospitalisation. This suggests that burden studies not accounting for post-discharge deaths may underestimate the true number of deaths due to SARI or influenza. Among children aged <18 years, factors like difficulty breathing, length of hospitalisation, heart diseases, and age were associated with an increased risk of death within 30 days of discharge. For adults aged ≥18 years, factors such as difficulty breathing, COPD, ICU admission, and age were linked to an increased risk of death within 30 days of discharge. Despite many discharge dispositions indicating full recovery, deaths occurred outside the hospital during the 30 days post-discharge, emphasising the need for post-discharge follow-up and surveys to better quantify true SARI deaths.

The mortality proportion among patients with SARI in our study was notably higher compared to a study conducted in China, where 4% of patients with SARI succumbed, with no statistically significant difference in the percentage of in-hospital deaths (2%) and deaths within 30 days of discharge (2%).[11] Another study focused on Sub-Saharan African countries[4] reported that approximately 6% of SARI-associated deaths occurred in hospitals, a rate higher than the 1.5% of in-hospital deaths observed in our study. Furthermore, a study conducted in Guatemala revealed that 5.9% of patients with SARI died in the hospital, and 2.7% of deaths occurred within 7 days of discharge.[12] These findings underscore the importance of considering both in-hospital and post-discharge deaths when estimating the overall incidence of SARI mortality.

Our data indicated that influenza virus infections may be associated with approximately one in ten in-hospital deaths (13%) and post-discharge deaths (10%), with 59% (65/111) of influenza deaths occurring after discharge. Therefore, both in-hospital and post-discharge deaths should be considered to understand the true burden of influenza-associated SARI deaths. Our findings underscore the importance of pharmaceutical interventions, such as antiviral medications and seasonal influenza vaccination, to reduce mortality due to influenza virus infection.

Two-thirds of post-discharge deaths occurred in the patient's home. These findings are consistent with a previous study in Bangladesh, which suggested that 60% of ARI-associated deaths occurred at home.[2] This finding is also consistent with a South African study,

Model	Factors	aHR	95% CI	p-value
Model-1	Age in year	1.04	1.04–1.05	<0.001
	Sex (male)	1.60	1.26–2.02	<0.001
Model-2	Smoking	2.61	2.13–3.19	<0.001
Model-3	COPD	3.65	2.95–4.52	<0.001
	Asthma	1.43	1.09–1.89	0.010
	Diabetes	1.55	1.12–2.13	0.007
	Heart diseases	1.45	0.96–2.20	0.079
	Hypertension	1.26	0.96–1.66	0.095
	Influenza virus detected	0.45	0.33–0.61	<0.001
Model-4	Duration of symptoms prior to admission in days	1.05	1.00–1.10	0.069
	Length of hospital stay in days	1.03	1.01–1.05	0.012
	Difficulty breathing	4.29	3.31–5.56	<0.001
	ICU support	7.18	2.68–19.25	<0.001
Model-5	Smoking	1.30	0.98–1.73	0.070
Model-6	COPD	1.71	1.35–2.16	<0.001
	Asthma	1.13	0.85–1.49	0.404
	Diabetes	1.34	0.98–1.85	0.070
	Influenza virus detected	0.48	0.36–0.66	<0.001
Model-7	Length of hospital stay in days	1.02	0.99–1.05	0.320
	Difficulty breathing	2.28	1.73–2.99	<0.001
	ICU support	5.19	1.92–13.99	<0.001

Note: *adjusted hazard ratio (aHR), confidence interval (CI), chronic obstructive pulmonary disease (COPD), intensive care unit (ICU).* In Models 1–4, we presented the direct relationship between the outcome and explanatory variables/potential predictors at each level without adjusting for variables from other levels. In Model 5, the covariates included the smoking variable along with age and sex variables. Model 6 incorporated COPD, asthma, diabetes, and influenza virus detected variables, along with the covariates heart diseases, hypertension, smoking, age, and sex variables. Model 7 included length of hospital stay in days, difficulty breathing, and ICU support variables, along with the covariates COPD, diabetes, duration of symptoms prior to admission in days, influenza virus detected, and age variables. The results for adjusted variables are detailed in Table S5. Data collection on self-reported comorbidities (e.g., asthma, COPD, diabetes, hypertension, and heart diseases) commenced in May 2013 (N = 10,046).

Table 3: **Factors associated with post-discharge deaths among adults aged ≥18 years (N = 12,846) who were admitted to selected hospitals in Bangladesh.**

which showed that 63% of influenza-associated deaths occurred outside the hospital.[13] A systematic review of 24 studies on paediatric deaths in developing countries showed that two-thirds of deaths after discharge occurred at home.[14] Our study, along with these other studies, suggests it is important to strengthen post-discharge follow-up and care to improve health outcomes and reduce preventable death.

We observed that half of post-discharge deaths occurred within 7 days of discharge. Furthermore, 17% of deaths occurred within 24 h of discharge, and many of these patients had a discharge disposition of partially or fully recovered, underscoring the risks of early discharge for patients with SARI. This is consistent with other studies that suggest high mortality during the transition from hospital discharge to home.[15–20] It is possible that patients who died towards the end of the 30-day post-discharge period may have had new infections unrelated to the reason for admission. It is also possible that the proportion of deaths in the group lost to follow-up (N = 2965; creating challenges for follow-up) was greater than in the group that was followed up. If this were true, our numbers may underestimate the number of deaths related to SARI.

Our study identified several demographic and clinical characteristics during hospital stay that were associated with death during the post-discharge period. We found a higher proportion of post-discharge deaths among children <1 year, adults aged ≥65 years, and patients with comorbid conditions, which was consistent with other studies of post-discharge mortality.[5,21–23]

We observed just over one-third of patients who died during the post-discharge period (36%, 233/633) had a medical record note of being fully recovered at initial discharge. Of these, almost half (45%) died after 2 weeks of discharge. It is possible that patients who died after 2 weeks of initial discharge may have had new infections. Our study also observed that two-thirds of post-discharge decedents had medical record notes documenting a request for discharge by the patient/their family or on the advice of a physician or with a referral to a specialised hospital. Patients may be discharged before fully recovered for several reasons, including presumed recovery,[21] inability to afford further hospitalisation, or exhaustion of treatment options at the hospital. A health and demographic survey in Bangladesh found that the most common reasons for requesting discharge were family members' perception

that the patient's health would not improve (52%), inability to pay hospital and treatment costs (17%), perceived improvement in health status (8.7%), or misjudgement of illness severity (4.3%).[24] Overcrowded hospitals might prematurely discharge patients to free bed space.[25,26] Finally, in Bangladesh, anecdotally, many patients who believe that they are going to die at any moment prefer to return to their homes rather than stay in the hospital.[24] In Bangladesh, there are no referral guidelines for physicians; hence, physicians must subjectively assess when to refer patients for further treatment. Hospital discharge and referral criteria for patients with SARI could be developed, and physicians trained to improve transfer and post-discharge outcomes.[27] Formative studies to better understand reasons for premature discharge in Bangladesh and to find ways to improve health outcomes of patients with SARI could help identify strategies to reduce post-discharge deaths.

Our study findings provide insights into the post-discharge outcomes for patients with SARI in Bangladesh. While the demographic and clinical characteristics of our study patients are reflective of the regional population, caution is warranted when generalizing to other settings. The generalizability of our results may be relevant to LMICs with similar contexts, however, variations in healthcare delivery systems, cultural practices, and patient behaviors across regions could impact applicability. Future studies should replicate this work in diverse settings to confirm universal relevance of the identified risk factors and to develop broadly applicable interventions. The standardized data collection methods and validated tools used in our study enhance the potential relevance of our findings in other settings, although adaptations may be necessary for local differences. We encourage cautious interpretation when applying these results beyond the context of our study.

Our study exhibits several strengths, utilizing a comprehensive approach over an eight-year span for a multicentre prospective observational study in Bangladesh. The inclusion of sites across Bangladesh, a large number of participants of all age, and an extended follow-up period after discharge fills a knowledge gap, shedding light on the imperative for interventions beyond the hospitalization phase. Our research found that around 5% of SARI patients admitted to hospitals died during the study period, with nearly two-thirds of these deaths occurring after discharge. This finding underscores the significance of recognizing the extended risk period for SARI-related deaths and identifying specific factors associated with post-discharge mortality. The study's prospective design and meticulous data collection provide a platform for future efforts to improve patient care after discharge. By utilizing this platform, we can develop interventions that enhance continuity and ultimately improve post-hospitalization survival.

Our study had several limitations. First, we were unable to reach all patients with SARI after discharge; 13% of patients with SARI were lost to follow-up, which may bias estimates of post-discharge deaths. Second, causes of post-discharge deaths were reported by family members, which may not accurately indicate the actual cause of death. Third, there is a significant information gap between post-discharge death circumstances and in-hospital death circumstances, and family members were unable to provide more details about the course of illness surrounding post-discharge deaths. Fourth, we obtained data from our routine influenza surveillance platform; thus, we were not able to have specific risk factor data among children aged <5 years for post-discharge deaths, such as nutritional status, anthropometric measurements, and the social status of the family members of the younger children. Fifth, we only tested patients with SARI for influenza viruses and do not know the potential contribution of other aetiologies to the occurrence of both in-hospital and post-discharge deaths.

Approximately 5% of patients with SARI died; of these, two-thirds occurred within 30 days post-discharge, indicating that deaths occurring after discharge may be unrecognised contributors to the true SARI mortality burden in Bangladesh. Post-discharge mortality was higher in infants and older adults, and most deaths occurred within the first week after discharge. The presence of heart diseases, difficulty breathing, and longer hospital stays was associated with post-discharge deaths among children aged <18 years. For adults aged ≥18 years, the presence of COPD, difficulty breathing, and ICU admission was associated with post-discharge deaths. These findings suggest the utility of monitoring patients following discharge and reducing the occurrence of premature discharge may improve health outcomes of patients and potentially prevent post-discharge deaths. However, to reduce the burden of influenza-associated mortality, seasonal influenza vaccination is recommended. Also, future studies are needed to explore further the reasons for premature discharge, causes of post-discharge SARI deaths, and to identify preventable post-discharge deaths. Findings from such studies would inform resource allocation and interventions in Bangladesh to improve patient outcomes after discharge.

Contributors

Study conceptualisation: MAI, MZH, MR, WWD, EAB, ADL, FC; Methodology: MAI, MZH, MR, WWD, EAB, ADL, MAA, ZA, FC; Software: MAI, MZH, MKA; Investigation: MAI, MZH; Resources: MAI, MZH; Validation: MAI, MZH; Formal analysis: MAI, MZH; Data curation: MAI, MZH, MKA; Original draft preparation: MAI, MZH, MR, WWD, EAB, ADL, FC; Supervision: MAI, MZH, FC; Funding acquisition: MAI, MZH, FC; Visualisation: MAI, MZH; Project administration: MAI, MZH, FC; Writing—review and editing: MAI, MZH, MAA, ZA, SC, MKA, MR, MZR, SM, MSU, TS, MSF,MR, WWD, EA, ADL, FC. All authors had access to the data and critically reviewed the manuscript for important intellectual content and approved the final

version. MAI, MZH and FC had the final responsibility to submit for publication.

Data sharing statement

According to data policies of the contributing institutions, to protect intellectual property rights the primary data cannot be made publicly available by the authors. The data may be made available upon reasonable request to the Institutional Data Access Committees of the contributing institutions.

Editor note

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Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2024.100363.

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