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Association between COVID-19 Disease and Mortality after Hip Fracture Surgery in Elderly: A Multicentre National French Survey

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Abstract

Background: Although COVID-19 and major surgery have been linked to mortality, controversy exists about the risk of higher mortality in the context of hip fracture. The objective of this study was t**o** assess the association between mortality (30th day postoperatively) and hip fracture surgery in patients with COVID (PCR+ 30 days) before surgery.

Methods: This was a population-based, retrospective cohort study of adults undergoing hip fracture surgery between March 1st and December 31st, 2020, at private or public hospitals in France. Patients were adults, >65 yrs, with hip fracture admitted for surgery. SARS-CoV-2 infection within 30 days before surgery was recorded. Main outcome was mortality within 30 days after surgery. Secondary outcomes included univariate and multivariate analysis of the association between subject characteristics and death at 30 days.

Results: Among 73,661 patients with hip fracture (mean age 85 ± 7.9 yrs, 76% women) who met study entry criteria, overall mortality at 30 days was 4.8%. Among them, mortality in non-COVID patient was recorded for 3 304 (4.58%). For patients with SARS-CoV-2 infection (1,505 patients), mortality was recorded for 228 (15.15%; *p(Khi-2)* <0.0001. The pair hip fracture and COVID-19 were associated with higher risk of mortality: OR, 3.72; 95% CI, 3.21-4.30; *P*<00.1.

Conclusion: Among adults undergoing hip fracture surgery, COVID-19 infection was associated with a greater risk of 30-day mortality.

Keywords: Hip fracture; COVID-19; Mortality; Surgery

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Introduction

Hip fracture in the elderly is a worldwide public health issue and a medical challenge for early postoperative rehabilitation [1]. More than 2 million people are treated annually with an annual incidence between 100 and 300/100.000 (USA, Europe, China), resulting in a cost of billion dollars and a strain on most surgical facilities [2,3]. In this context, an early surgical management of patient with fracture within the first 24 h to 48 h has been shown to reduce morbidity, length of hospital stays and mortality (at 30 days: 5% to 10%) [4]. During the COVID-19 pandemics, a higher risk of 30-day mortality has been reported in patients with pre-operative SARS-CoV-2 infection diagnosed from 0 to 6 weeks before surgery compared with patients who did not have a pre-operative SARS-CoV-2 infection [5,6]. However, this risk seems to disappear in patients diagnosed with SARS-CoV-2 ≥ 7 weeks before surgery [6]. These findings led to propose delayed elective surgery when the benefit-risk ratio was acceptable (cancer, cardiac surgeries) [6,7]. However, delaying surgery in COVID-19 patients (with high risk of immune and thrombotic disorders) with hip fracture could be questionable as the risk related to COVID-19 could be counteracted by the risk delayed surgery [1-4]. Recently, several brief report and meta- analysis highlighted higher risk of mortality after hip fracture associated with SARS-CoV-2 infection [8,9]. For assessing the mortality risk related to hip fracture surgery associated with COVID-19 on large cohort over first and second wave, we used the French national hospital discharge records database for comparing the 30-day postoperative

mortality in patients with hip fracture and with or without a hospitalization for SARS-CoV-2 infection in the 30 previous days before surgery [6].

Methods

Study design and data source

The present study used data from the French national hospital discharge records database (resulting from the "French Prospective Payment System", I), which systematically collects administrative and medical information related to all patients hospitalized and all hospital stays in private and public hospitals [10]. It is routinely completed for the purpose of care reimbursement, supporting its suitable accuracy and exhaustive data collection. The available data are age, gender, entry and discharge dates, diagnoses' codes associated to the hospitalizations (according to international classification of diseases (ICD, Tenth Revision, Clinical Modification (ICD-10-CM)), death during a hospitalization. Concerning patients and stays, data are entered by physician daily and/or when the patient is discharged The French Ministry of Health (Assurance Maladie) regularly controls the quality of the database. The researchers and health institutions who collect their data according to the current guidelines could access to the complete database [10]. The retrospective design of prospectively and anonymously collected data was approved by the Institutional Review Board of the University Hospital Caremeau, Nimes, France (IRB 2021.05.21: 21.0034) and registered on Clinical Trials (NCT NCT04944329). According to the French current law, no informed consent was required [11]. STROBE recommendations for observational studies were followed.

Patients with hip fracture, and with or without a SARS-CoV-2 disease

We included patients ≥ 65-year-old with hip fracture hospitalization recorded between March 1st and December 31st, 2020, detected through ICD-10 diagnosis codes that begin with femoral neck fracture, trochanter fracture or subtrochanteric fracture, and with a DRG Codes (Diagnosis Related Group) code indicating a surgical procedure (hip prostheses for recent trauma, hip and femur surgery for recent trauma). Patient with hip fracture hospitalization without a care code indicating a surgical procedure were excluded. In these patients, we searched for hospitalizations with SARS-CoV-2 diagnostic that occurred within 30 days before the date of hospital admission for hip fracture. For this we used the following codes: COVID-19 respiratory form identified virus, COVID-19 respiratory form unidentified virus, COVID-19 carrier of SARS-CoV-2 asymptomatic identified virus, COVID-19 other clinical forms identified virus, COVID-19 other clinical forms unidentified virus. Patients with only a code "Other examinations and observations related to the epidemic COVID-19" were not retained as positive for SARS-CoV-2 disease.

Primary endpoint

The primary end point was in-hospital mortality within 30 days of the date of hospital admission for hip fracture. This criterion is collected exhaustively in the French national hospital database.

Secondary endpoint

Secondary outcomes included univariate and multivariate analyses of the association between subject characteristics and death at 30 days.

Statistical analysis

The patient characteristics are described with absolute numbers and proportions for categorical variables and with means and Standard Deviations (SD) for quantitative variables. Comparisons between groups were performed using Wilcoxon test for quantitative variables and the Chi-square for qualitative variables. To analyze the effect of SARS-CoV-2 infection on 30-day postoperative mortality independently of potential confounders, we performed univariate and multivariate logistic regression models. The results are presented with odds ratios and their 95% confidence intervals. Interactions between SARS-CoV-2 infection and other available variables were all tested in successive multivariate logistics models. All analyses were conducted by the medical statistics department of the Nimes University Hospital using SAS software (V.9.4, SAS Institute, Cary, NC, USA). A two-sided p value of <0.05 was considered to indicate statistical significance.

Results

During the study period, 73,661 patients underwent a hip fracture surgery in France (Table 1) and a SARS-CoV-2 infection was diagnosed within 30 days before surgery in 1,505 (2.04%) patients of them. Table 1 shows patients characteristics according to COVID and Non-COVID status. Patients with COVID were older, with a higher Charlson comorbidity Index score and had a longer length of stay in hospital. The geographical location of traumatic fall (at home: 93% for Non-COVID *vs.* 88 % for COVID), Fracture location and type of surgical interventions and time for surgery were similar. In 1505 COVID patients (2.04%), the SARS-CoV-2 infection was diagnosed during the Hip fracture hospitalization. The mean time from hospitalization with a diagnosis of SARS-CoV-2 to hospitalization for hip fracture was 1.73 (SD:5.77) days.

Primary outcome

In patients with hip fracture, 3,532/73,661 patients (4.8%) died in the first 30-day postoperative days. The 30-day postoperative mortality was significantly higher in patients with SARS-CoV-2 infection (228/1505 (15.15%) *vs.* 3305/72156 (4.58%), p value <0.001, crude OR: 3.72, 95% CI [3.21-4.30]). After adjustment for age, sex, Charlson comorbidity Index score, fracture location, and type of surgery, the SARS-CoV-2 infection within the 30 preoperative days was associated with a higher mortality rate (adjusted OR: 3.42 95% CI: 2.94–3.97). Table 2 and 3 show the factors associated with a higher mortality rate. In multivariate analyses age, sex, Charlson comorbidity Index score, fracture location, and type of surgery were independently associated with 30-day postoperative mortality (Table 3). No effect statistical interaction of SARS-CoV-2 infection with other variables available (notably age) was found to be statistically significant. The interaction with sex showed a statistical trend (p=0.07), with a rather stronger increase in risk related to SARS-CoV-2 infection in men (OR for SARS-CoV-2=4.09 95% CI=3.22-5.20) than in women (OR SARS-CoV-2=3.09 95% CI 2.53-3.74).

Discussion

In this retrospective study using the French database of 73,661 patients with hip fracture, a SARS-CoV-2 infection within 30 previous days of surgery was associated with a 3-fold higher mortality rate (15.15%) compared to non-COVID-19 patients. This first large cohort is the first one that confirmed recent brief reports and meta-analysis that demonstrated an increased risks of 30-day mortality (32.23% COVID-19 + death *vs.* 8.85% COVID-19 - death) and

Table 1: Characteristics of the subjects included in the study, overall and according to the presence of a hospitalization for COVID in the 30 days preceding admission for hip fracture surgery.

	Overall N=73661	Non-COVID N=72156	COVID N=1505	P value
Age				
Mean (std)	85.0 (7.9)	84.9 (8.0)	86.3 (7.4)	<0.001
Sex				
Women n(%)*	55 881 (75.9%)	54 745 (75.87%)	1 136 (75.48%)	0.727
Fracture				
Femoral neck n(%)*	43 797 (59.5%)	42 908 (59.47%)	889 (59.07%)	0.399
Trochanter n(%)*	26 045 (35.4%)	25 497 (35.34%)	548 (36.41%)	
Subtrochanteric n(%)*	3 819 (5.2%)	3 751 (5.20%)	68 (4.52%)	
Surgical intervention				
Hip prosthesis n (%)*	32 990 (44.8%)	32 337 (44.82%)	653 (43.39%)	0.27
Other n(%)	40 671 (55.2%)	39 819 (55.18%)	852 (56.61%)	
Charlson index				
Mean (std)	1.2 (1.8)	1.2 (1.8)	1.5 (1.9)	0.01
Length of stay (in days)				
Mean (std)	9.2 (6.6)	9.1 (6.5)	13.3 (10.9)	<0.001
Death				
Death n(%)*	3 532 (4.8%)	3 304 (4.58%)	228 (15.15%)	<0.001
Mean (std)	4.7 (6.9)	4.8 (7.0)	2.6 (4.7)	<0.001

*column percentage

Table 2: Characteristics of the subjects according to death in the 30 days following admission for hip fracture surgery**.**

	Survival N(%)* or Mean (std) N=1505	Death 30 days N(%)* or Mean (std) N=72156	P value
Age			
Mean (std)	84.8 (8.0)	88.1 (7.0)	<0.001
Sex			
Women	53 822 (96.32%)	2 059 (3.68%)	<0.001
Men	16 307 (91.72%)	1 473 (8.28%)	
Fracture			
Femoral neck	41 840 (95.53%)	1 957 (4.47%)	<0.001
Trochanter	24 673 (94.73%)	1 372 (5.27%)	
Subtrochanteric	3 616 (94.68%)	203 (5.32%)	
Surgical intervention			
Hip prosthesis	31 525 (95.56%)	1 465 (4.44%)	<0.001
Other	38 604 (94.92%)	2 067 (5.08%)	
Charlson index			
Mean (std)	1.2 (1.8)	1.9 (2.2)	<0.001
Average length of stay			
Mean (std)	9.2 (6.7)	8.8 (5.8)	<0.001
COVID Infection			
Yes n(%)	1 277 (84.85%)	228 (15.15%)	<0.001
No	68 852 (95.42%)	3 304 (4.58%)	
Time between COVID and admission (in days)			
Mean (std)	1.9 (6.1)	0.7 (3.3)	<0.001

*row percentage

inpatient mortality (29.33% *vs.* 2.62%) among COVID-19 + patients with Odds Ratio (OR) of 4.84 (95% CI: 3.13-7.47, p<0.00001) and 15.12 (95% CI: 6.12-37.37, p<0.00001) [8,9]. With COVID-19 pandemic, performing surgery in the COVID setting has been widely debated. Indeed, all studies carried out during COVID-19 pleaded for postponing an elective surgery, when possible, for the patient, leading

Table 3: Univariate and multivariate analyses of the association between subject characteristics and death at 30 days.

		OR	CI 95%	p value	AOR*	CI 95%	p value
COVID Infection	No	1	ref		1	ref	
	Yes	3.72	(3.22; 4.30)	<0.0001	3.43	(2.95; 3.98)	<0.0001
Fracture	Femoral neck n(%)*	1	ref		1	ref	
	Trochanter n(%)*	1.19	(1.11; 1.28)	<0.0001	1.12	(1.01; 1.23)	0.025
	Subtrochanteric n(%)*	1.20	(1.04; 1.39)	0.016	1.15	(0.97; 1.36)	0.099
Age	(In years)	1.06	(1.05; 1.06)	<0.0001	1.07	(1.06; 1.08)	<0.0001
Charlson index	Charlson 0	1	ref		1	ref	
	Charlson 1	1.76	(1.52; 2.05)	<0.0001	1.63	(1.40; 1.90)	<0.0001
	Charlson 2	1.52	(1.39; 1.66)	<0.0001	1.37	(1.25; 1.50)	<0.0001
	Charlson 3	2.52	(2.23; 2.84)	<0.0001	2.05	(1.82; 2.32)	<0.0001
	Charlson 4	2.43	(2.13; 2.77)	<0.0001	2.05	(1.79; 2.34)	<0.0001
	Charlson 5	3.31	(2.80; 3.92)	<0.0001	2.62	(2.21; 3.11)	<0.0001
	Charlson 6	3.11	(2.72; 3.55)	<0.0001	3.04	(2.65; 3.49)	<0.0001
Surgical intervention	Other	1	ref		1	ref	
	Hip prosthesis	0.87	(0.81; 0.93)	<0.0001	0.99	(0.90; 1.10)	0.93
Sex	Men						
	Women	0.42	(0.40; 0.45)	<0.0001	0.40	(0.37; 0.43)	<0.0001

*AOR: Adjusted Odds Ratio. All factors in the table were entered in the multivariate logistic regression model

to recommend to postpone surgical procedure in patients with recent SARS-CoV-2 infection [6,7]. In patients with femoral neck fracture, this guideline could be challenged as postponing surgery induces an excess of mortality. As described recently, accelerated (<6 h) *vs.* standard care (<48 h) in hip fracture surgery did not significantly lower the risk of mortality or a composite of major complications [2]. In the opposite, current guidelines pointed out that a delay of more than 48 h was associated with an increased risk of mortality medical complications among patients with hip fracture [12-14]. In a national cohort of 73.661 elderly patients with hip fracture, the present study confirms a higher mortality rate in COVID-19 patients, considered as an additional mortality factor. In such conditions, the 15% mortality was 3-fold higher than in non-COVID-19 patients. Age and a poor baseline vital status were the other factors associated with a higher mortality rate. Even if French national database is regularly checked meaning that it could be considered as to an exhaustive and accurate, using it is always challenging and can be a potential limitation of the study as SARS-CoV-2 patients were identified with diagnostic code. Indeed, asymptomatic or infected patients earlier than 30 days before surgery might have been not tested and considered non-infected. However, this classification potential bias would have led to dilution effect and an underestimation of the effect of SARS-CoV-2 on mortality. On the other hand, given the purpose of the administrative database and its regular verification, we can assume that information on hip surgery is exhaustive and accurate during the study period. The main finding of the present study is the absence of modulation of the effect of SARS-CoV-2 infection according to patient characteristics meaning that the SARS-CoV-2 infection associated mortality risk remains constant whatever the patient and his(her) risk factors. Therefore, patients with multiple risk factors, the associated risk will be multiplied by 3 leading to a very high associated mortality rate. For instance, a patient with several risk factors and an already high absolute risk of death in the absence of SARS-CoV-2 infection (e.g., 20%) would have his absolute risk of death increased dramatically in the presence of infection (20%*3.4=68%). This may also be the population that would potentially benefit most from close monitoring for SARS-CoV-2 infection in the post-procedure period. Even the study focuses on 2020, our study period excluded the third wave (spring 2021) vaccination campaign effects and science updates, which might affect the primary outcome. Due to the deep impact of COVID-19 in health care organization, time before surgery such as hospital length of stay could have been impacted, compared to pre-COVID-19 outbreak. In clinical practice, there are several reasons why a COVID patient's hip fracture surgery might be postponed: The need for an additional respiratory assessment, waiting for the PCR test, unavailability of space in the hospital or operating theatre. Among adults undergoing hip fracture surgery and because COVID-19 infection was associated with a greater risk of 30-day mortality, a dedicated COVID-19 perioperative pathway with early screening and surgical management would be an efficient key to enhanced postoperative recovery and mortality. In conclusion, recent or current SARS-CoV-2 infection is associated with a 3-fold higher mortality rate in elderly patients with hip fracture surgery.

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