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Excess Mortality in a Nephrology Clinic during First Months of Coronavirus Disease-19 Pandemic: A Pragmatic Approach

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Abstract

BACKGROUND: Excess mortality is defined as mortality above what would be expected based on the non-crisis mortality rate in the population of interest.

AIM: In this study, we aimed to access weather the coronavirus disease (COVID)-19 pandemic had impact on the in-hospital mortality during the first 6 months of the year and compare it with the data from the previous years.

METHODS: A retroprospective study was conducted at the University Clinic of Nephrology Skopje, Republic of Macedonia. In-hospital mortality rates were calculated for the first half of the year (01.01–30.06) from 2015 until 2020, as monthly number of dead patients divided by the number of non-elective hospitalized patents in the same period. The excess mortality rate (p-score) was calculated as ratio or percentage of excess deaths relative to expected average deaths: (Observed mortality rate–expected average death rate)/expected average death rate *100%.

RESULTS: The expected (average) overall death mortality rate for the period 2015–2019 was 8.9% and for 2020 was 15.3%. The calculated overall excess mortality in 2020 was 72% (p_{score} 0.72).

CONCLUSION: In this pragmatic study, we have provided clear evidence of high excess mortality at our nephrology clinic during the 1st months of the COVID-19 pandemic. The delayed referral of patients due to the patient and health care system-related factors might partially explain the excess mortality during pandemic crises. Further analysis is needed to estimate unrecognized probable COVID-19 deaths.

Introduction

The World Health Organization (WHO) has recognized the spread of coronavirus disease (COVID)-19 as a pandemic in March 2020 [1]. Authorities worldwide have implemented preventive measures, restrictions, lockdowns, and facility closures to slow the spread of the disease. Still, over 690,000 deaths worldwide were registered [2]. Excess mortality is defined by WHO [3] as: "Mortality above what would be expected based on the non-crisis mortality rate in the population of interest. Excess mortality is, thus, mortality that is attributable to the crisis conditions. It can be expressed as a rate (the difference between observed and non-crisis mortality rates), or as a total number of excess deaths." It is used to measure the mortality impact of a crisis when not all causes of death are known.

Hospital mortality has been used to assess the quality of care in our University Clinic of Nephrology (UCN). The annual in-hospital mortality rate which is being regularly referred to as the Ministry of Health (MOH), has been stable around 6% in the previous several years [4]. This healthcare unit is providing nephrology tertiary care for around two million citizens. It treats over 20000 outpatients per year and more than 2300 in-hospital patients. It provides over 500 emergency dialysis sessions, over 1500 vascular access interventions covering complications for almost all hemodialysis patients in the country [5]. Annually hundreds of renal [6], [7] and prostate biopsies are performed as elective or urgent procedures. Almost all Macedonian chronic kidney disease (CKD) patients initiate chronic hemodialysis program at our clinic and referred to local dialysis centers thereafter. Annually that number is around 300 patients [8].

The COVID-19 pandemic did not spare Macedonia. The first recognized case was known to be imported from Italy and laboratory confirmed on 26th of February 2020 [9]. The MOH closely monitored and prevented the spreading of the virus with implemented strict protocols in the social area and the health care system. Patients were informed and medical doctors instructed to refer patients to tertiary level only in emergency. Substantial behavioral restrictions have been imposed mostly because of the decision to prioritize preventing clusters from spawning. Even though, in the end of June, more than 6000 people were infected and 298 patients had died [2]. In this period at our hospital, starting from March, all previously scheduled out-patient referrals and elective in-hospital diagnostic (biopsies) or vascular access interventions (arteriovenosus fistula/tunnelled catheter creations) were cancelled or postponed. Patients with nephrology emergency were referred from all over the country and screened for COVID-19 at admission by clinical examination and epidemiological questionnaire. Patients with high risk were isolated and tested with the polymerase chain reaction (PCR) technique. If positive, those were transferred to the dedicated COVID-19 hospitals. Hospital policy applied written protocol measures for prevention of spreading the disease and adequate stuff and patents protective equipment used according to the current MOH recommendations on COVID-19 disease. In hospital, mortality was monitored and notified.

In this study, we aimed to access whether the COVID-19 pandemic had an impact on in-hospital mortality during the first 6 months of the year and compare it with the data from the previous years.

Methods

A retro-prospective study was conducted at UCN Skopje, Republic of Macedonia. A pragmatic approach was used to determine in-hospital mortality rates for the first half of the year (01.01–30.06) from 2015 until 2020. The mortality rates were estimated as monthly number of dead patients divided by the number of non-elective hospitalized patents in the same period. The data were extracted from the hospital registry, the National Integrated Health Information System–My Term (Moj Termin) [10], and the diagnosis-related group system [11], both based on a central database of all public health services in the country for the hospital patients. All the patients that were registered for hospitalization at our clinic for any reason in the 6 years were analyzed; no patients were excluded from the study. Elective in-hospital procedures (programmed creation of permanent vascular access – AV fistula or tunneled central venous catheter, prostate biopsy, renal [native or transplant] biopsy, potential kidney donor, and recipient evaluations) were canceled during pandemic, which resulted in minimizing the number of hospitalizations. Furthermore, minor vascular access interventions were performed as single day ambulatory procedures. Therefore, the mortality rates for the previous years were also estimated only for non-elective hospitalizations. In addition, deaths were analyzed by time frame of occurrence in <24 and 48 h from admission. The number of initial hemodialysis patents was calculated per state population [5], [12].

The real-time reverse transcriptase-PCR (RT-PCR) technique was used to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from nasopharyngeal and oropharyngeal swabs as specimen from each patient. All tests were performed at the Laboratory for Virology, Institute of Public Health (IPH) according to protocols available on the WHO website [13]. Patients were tested at the discretion of the clinicians if clinical criteria or/and epidemiological linkage to COVID-19 disease were positive for close contact, prior, at admission, or during the hospital stay.

Statistical analysis was performed with SPSS 16.0 for Windows: Continuous variables are shown as mean values and categorical as percentages. The excess mortality rate (p-score) was calculated as ratio or percentage of excess deaths relative to expected average deaths: (Observed mortality rate–expected average death rate)/expected average death rate × 100%. The observed mortality rates were from 2020 and the expected from the period 2015 to 2019.

Results

During the previous 5 years, there were more than 1000 patients admitted each year in the first 6 months of the year (Table 1). The hospitalizations due to any elective procedure ranged from 20% to 38% and the rest (60–80%) were for urgent or other nephrological treatment. The half-annual all-cause mortality rates in non-elective cases were stable at 7.4–10.9%. Deaths in the first 24 h of admission ranged between 2.8% and 4.2% and in the first 48 h from 2.8% to 5.3%. In the current year of 2020, the admissions were rather halved in the first 6 months (497), including only 7% of elective cases. Almost exclusively (93%) were patients admitted for urgent or other non-delayable treatments. In 2020, the mortality rates raised up to 15.3% for all non-elective admissions, almost doubling for the 24 h deaths (6.0%) and for the deaths in the first 48 h (9.9%). As for the surviving patients, the number of incident dialysis patients through the period of all 6 years was stable around 150 patients or 75×10^{-6} per state population.

The expected (average) overall death mortality rate for the period 2015–2019 was 8.9%. For the patients that died in the first 24 h of admission, the average mortality rate for the same 5 years period was 3.3% and for the dead in the first 48 h 4.0%. The calculated overall excess mortality was 72% (p_{score} 0.72), then 79% (p_{score} 0.79) for mortality in the first 24 and 102% (p_{score} 1.02) in the first 48 h, respectively, for 2020 (Figure 1). Out of all 71 dead patients, 28 (40%) died in the first 24 h and 46 (65%) in the first 48 h in 2020.

Table 1: Admissions, mortality rates, and incident dialysis patients in the first 6 months from 2015 to 2020

Year (01th January–30th June)	2015	2016	2017	2018	2019	2020
All hospitalizations	1191	1250	1286	1061	1132	497
Non-elective (%)	757 (64)	856 (68)	819 (64)	659 (62)	905 (80)	463 (93)
Elective (%)	434 (36)	394 (31)	467 (36)	402 (38)	227 (20)	34 (7)
Mortality rates in non-elective cases (%)	60 (7.9)	74 (8.6)	61 (7.4)	72 (10.9)	88 (9.7)	71 (15.3)
Death cases (first 24 h) (%)	28 (3.7)	24 (2.8)	23 (2.8)	28 (4.2)	29 (3.2)	28 (6.0)
Death cases (first 48 h) (%)	31 (4.1)	30 (3.5)	23 (2.8)	35 (5.3)	39 (4.3)	46 (9.9)
In-hospital incident dialysis patients (per state population $\times 10^{-6}$) (%)	149 (74)	157 (78)	168 (84)	147 (73)	160 (80)	149 (74)

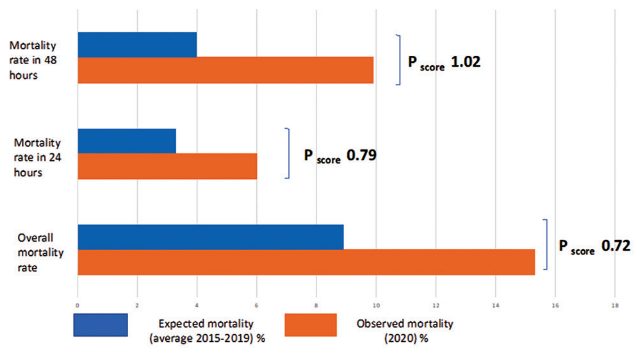

Figure 1: Excess mortality p-scores for 2020 regarding average mortality for 2015–2019.

Figure 2 compares the monthly in-hospital death rates for non-elective admissions in 2020 (red line), against each of the five preceding years. Soon after the detection of the first COVID-19 community case (26th of February), death rates increased rapidly. In <4 weeks, they almost doubled from 14.8% in March to 28.3% in April. In the following 2 months, the death rates were higher than 20%, exceeding the average rates in the same months in the previous 5 years (Table 2).

Table 2: Increasing monthly mortality rates in 2020 versus average death rates in 2015–2019

Mortality (%)	January	February	March	April	May	June
2015	9.6	9.1	4.1	8.0	8.8	8.1
2016	11.4	9.8	8.1	8.4	7.2	6.9
2017	11.0	3.0	6.5	5.7	7.6	11.1
2018	5.8	12.5	13.7	14.0	8.4	10.6
2019	7.4	10.6	12.2	6.6	15.0	7.2
Mean ± STDV (2015–2019)	9.0 ± 2.4	9.0 ± 3.6	8.9 ± 4.0	8.5 ± 3.2	9.4 ± 3.2	8.8 ± 2.0
2020	8.7	11.4	14.5	28.3	20.0	21.9

Figure 3 compares the monthly in-hospital first 48 h death rates for non-elective admissions in 2020 (red line) against each of the five preceding years. Death rates increased rapidly and achieved the pick in April, followed by numbers much higher than average ones in the preceding years (Table 3).

Table 3: Increasing monthly first 48 h mortality rates in 2020 versus average death rates in 2015–2019

Mortality (%) first 48 h	January	February	March	April	May	June
2015	5.6	3.3	3.3	2.7	6.9	3.5
2016	7.1	3.5	3.4	3.9	0.8	2.1
2017	4.9	0.6	3.9	3.4	2.3	1.7
2018	3.8	5.8	6.9	8.6	3.2	3.8
2019	3.9	3.5	5.2	2.9	7.1	3.2
Mean ± STDV (2015–2019)	5.1 ± 1.21	3.3 ± 1.64	4.5 ± 1.37	4.3 ± 2.19	4.0 ± 2.52	2.8 ± 0.81
2020	4.7	6.8	9.6	19.6	10.9	12.5

Figure 4 compares the monthly in-hospital first 24 h death rates for non-elective admissions in 2020 (red line) against each of the five preceding years. The curve climbed above 6% from February and maintaining Plato in the following months above 8%. Death rates were much higher than average ones in the preceding years (Table 4).

Table 4: Increasing monthly first 24 h mortality rates in 2020 versus average death rates in 2015–2019

Mortality (%) first 24 h	January	February	March	April	May	June
2015	4.0	4.1	3.3	1.8	5.8	2.9
2016	6.4	3.5	2.7	2.6	0.0	1.4
2017	4.3	4.2	1.3	3.4	2.3	3.4
2018	3.0	5.3	6.0	6.0	3.0	3.2
2019	3.1	3.0	5.0	2.7	5.7	3.4
Mean ± STDV (2015–2019)	4.2 ± 1.24	4.0 ± 0.78	3.6 ± 1.67	3.3 ± 1.45	3.4 ± 2.19	2.9 ± 0.76
2020	1.6	6.8	7.2	8.7	9.1	7.8

The number of hospital admissions in the first 2 months of 2020 was above 100 (Figure 5). A significant decline was observed from March, exceeding the lowest number in April (45). On the opposite, the RT-PCR testing for SARS-CoV-2 detection began at the beginning of April and raised along with the number of admitted patients.

From April 2020, the testing rate of the hospitalized patients was above 30% (Table 5). The patients that died we also partly tested in April 38%, May 27%, and 57% in June.

Table 5: Admissions, rates of RT-PCR tests for SARS-CoV-2 in all and the dead patients

2020	January	February	March	April	May	June
All admissions	134	104	91	45	55	64
All SARS-CoV-2 RT-PCR tests (rate)	0	0	0	15 (33%)	17 (31%)	25 (39%)
All deaths	11	10	12	13	11	14
SARS-CoV-2 RT-PCR tests in dead patients (rate)				5 (38%)	3 (27%)	8 (57%)

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, RT-PCR: Reverse transcriptase-polymerase chain reaction

In the first 6 months of 2020, there were 28 patients that died in the first 24 h of the hospital stay and only 2 (7.1%) were being tested for SARS-CoV-2 (Figure 6). Out of 46 patients that have died in the first 48 h of the hospital stay, 10 (21.7%) have been tested, and only one patient was positive. Other four positive patients were transferred to dedicated COVID-19 hospitals.

Discussion

During the COVID-19 pandemic, excess mortality was observed in many European countries [14] and reported in recent publications from all over the world [15], varying by states and regions. The analyzed data on excess mortality (the numbers of deaths over

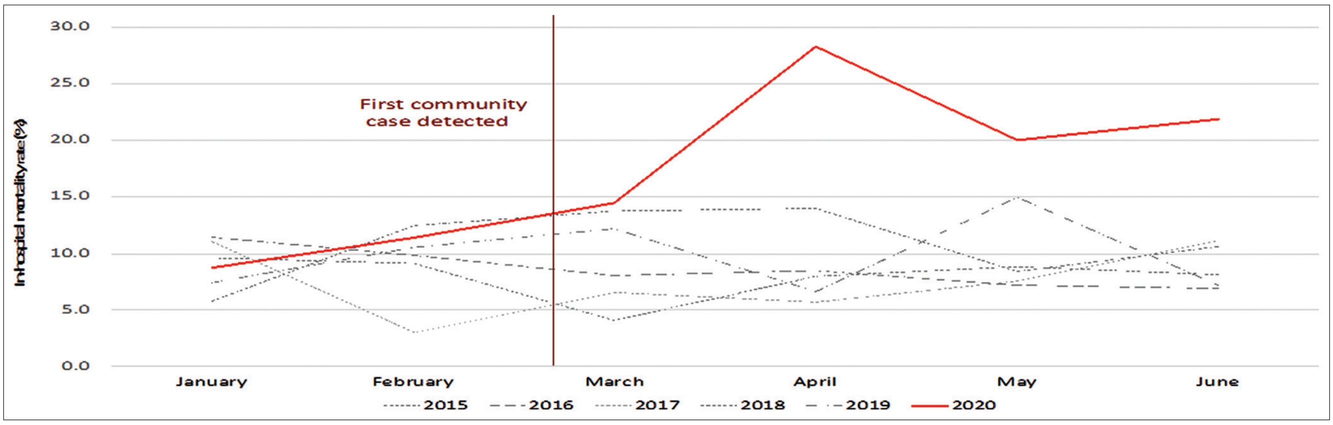

Figure 2: Monthly death rates in 2020 compared to the five preceding years for non-elective admissions

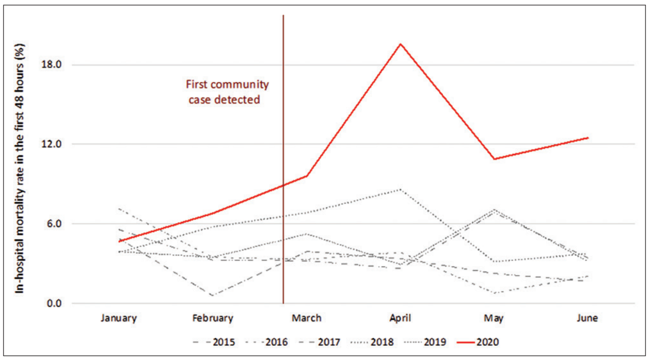

Figure 3: Monthly death rates in the first 48 h 2020 compared to the five preceding years for non-elective admissions

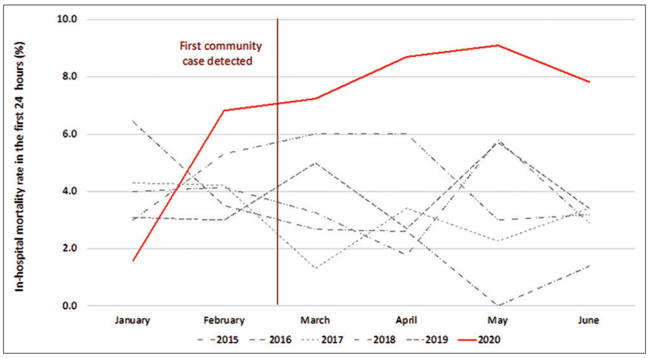

Figure 4: Monthly death rates in the first 24 h 2020 compared to the five preceding years for non-elective admissions

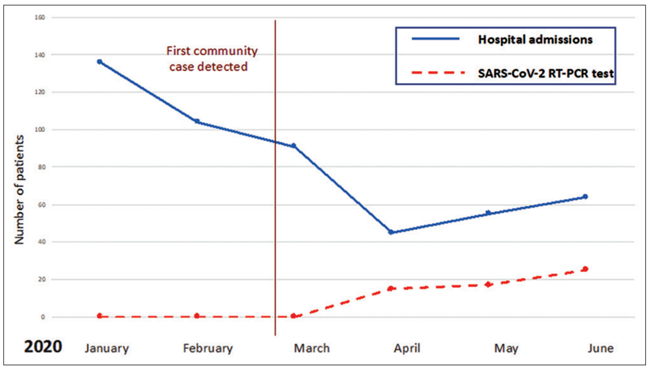

Figure 5: Hospital admissions and polymerase chain reaction testing for severe acute respiratory syndrome coronavirus-2 detection in hospitalized patients in 2020

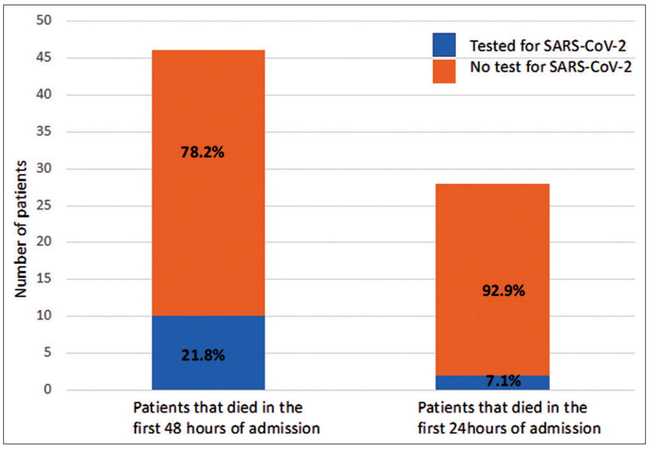

Figure 6: Proportions of performed severe acute respiratory syndrome coronavirus-2 tests regarding the time of the death

and above the historical average) across the globe have shown that numbers of deaths in some countries were more than 50% higher than usual [14]. In many countries, these excess deaths exceed reported numbers of COVID-19 deaths by large margins. In New York State, all-cause mortality rose from 2- to 7-fold above baseline at the peak of the pandemic, whereas 26% were unattributed to COVID-19 [16].

In this study, we have compared the in-hospital mortality rates in one nephrology clinic from the previous 5 years to the current year of 2020. The excess mortality exceeded 70%, resulting from sudden divergence from the excepted pattern, including decline in patients' hospitalizations and higher fatalities. This high mortality might be explained by several factors: Stress, avoidance of the health care system considering potential COVID-19 infection, delayed or unrecognized symptoms of kidney function deterioration with late admissions, and diagnostic uncertainties. We also have to account for the health care organizing changes.

Crises are generating stress to the general and populations with chronic diseases. During COVID-19 pandemic, WHO addressed the issue on global mental health and psychosocial considerations [17]. Stress implications for CKD initiation, progression, complications, and premature mortality are also well known [18]. Global lockdown, fear, lack of family connections, and low educational level of symptoms recognition might have caused delayed hospitalizations of patients with severe conditions. Our previous 5 years mortality study showed that more than 40% of dead patients from CKD were not aware of the disease or referred to a nephrologist ever [4]. Despite all the provided information about COVID-19, more than one-third of deaths from COVID-19 infection in our country occurred in the first 1–5 days after admission at hospitals and this high mortality was most probably due to the late referral or previous patients' reluctance for timely hospitalization [19]. However, patients educated and followed for CKD at our clinic, and those initiated on dialysis were timely referred even during COVID-19 lockdowns. This can be observed from the stable number of patients starting dialysis in the previous 5 years and during 2020. At best of our knowledge, there is no other publication on specific nephrology patients' mortality during this crisis to compare our data with and that is one limitation of our study. On the other hand, a dramatic hospital admission reduction for patients with acute myocardial infarctions has been witnessed in Asia [20], Europe [21], [22] and North America [23], associated with a parallel increase in hospital fatality and complication rates [24]. Those studies explained this phenomenon also by patients' related factors as stress, health care system reorganizations, and unrecognized COVID-19 deaths, referring to the need of education as prevention [25].

The highest pick of mortality at our clinic was observed in April, which is in line with mortality picks in nearly all European countries suffering from the outbreak in March 2020 and global lockdown [14]. Furthermore, 64% of all deaths occurred in only 48 h after admission. Considering the limited time before death, the number of first and repeated tests performed and sensitivity of the tests, there have might been a number of deaths caused by the virus that were not counted. One reason might be the detectability and clearance of the viral RNA [26]: Patients with mild symptomatology do not refer to the doctor in a timely fashion for being tested; also, the virus may be detectable in the upper respiratory tract 1–3 days before the onset of symptoms with the highest concentration around the time of symptom onset, and clearance of the virus for several days in some patients, while in other patients it can be detected for several weeks even months. As a limitation of our study, many patients were not tested, and in those that were tested, only one test was performed because of death. According to literature [26], [27] and the "National guidance for interpretation of the COVID-19 test results" published by the IPH since March 2020 [28], subsequent testing is recommended for firstly negative patients as well as considering other types of samples, not only from the upper respiratory tract. Recent systematic reviews of the accuracy of SARS-CoV-2 tests reported false-negative rates of between 2% and 29% (equating to sensitivity of 71–98%), based on negative RT-PCR tests which were positive on repeat testing [29], [30]. Furthermore, accuracy of viral RNA swabs in clinical practice varied depending on the site and quality of sampling [31], especially in patients with intestinal form of COVID-19 infection [32], where the respiratory infection was not confirmed by nasal swabs detection. Considering all these findings, we speculate that there might be some unrecognized or unconfirmed probable COVID deaths [33] among our patients, which implies a need of further analysis. If some of the patients were recognized with COVID-19 infection, part of them might be transferred to dedicated COVID-19 clinics, and the mortality rate would be lower, which also limits our study.

Nevertheless, the importance of our study is in the pragmatic approach by seeing the real striking data on the higher mortality rates during the pandemic from the registry data which elucidates the need of more knowledge about the novel virus and global pandemic circumstances.

Conclusion

In this study, we have provided clear evidence of high excess mortality at our nephrology clinic during the 1st months of the COVID-19 pandemic. Severely ill patients mostly died in the early 48 h of admission, limiting the time for diagnostic and therapeutic options. The delayed referral of patients due to the patient and health care system-related factors might partially explain the excess mortality during pandemic crises. Education of patients in recognizing symptoms of life-threatening conditions and seeks appropriate care on time remains crucial during the COVID-19 pandemic. Further analysis is needed to estimate unrecognized probable COVID-19 deaths.

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