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Maternal deaths among patients with cancer in the United States

Ying Chen, MD[a], Yongqiang Zheng, MD[b,c], Kaixu Yu, MD[d], Bian Wu, MD[b,*]

Abstract

Our objective was to characterize the risks of maternal deaths in cancer patients compared to the general population using a large population-based cohort.

Female patients with a cancer first diagnosed at ages 15 to 39 years between 2000 and 2016 (N = 240,561) from the surveillance, epidemiology, and end results database were extracted, among which 165 maternal deaths were observed.

We found Hispanic ethnic groups, advanced cancer stage, receiving chemotherapy were associated with a higher risk of maternal deaths compared to the general the United States population. Patients with cancers of the respiratory system were at the highest risk of maternal deaths, followed by cancers of the digestive system, and hematological malignancies.

Abbreviations: CI = confidence interval, HR = hazard ratio, SEER = surveillance, epidemiology, and end results, SMR = standardized mortality ratio, US = the United States.

Keywords: cancer, maternal deaths, pregnancy, risk factors, standardized mortality ratios

1. Introduction

The past decades witnessed a rising trend of delaying childbearing, leading to a potential increasing occurrence of cancer before or after a pregnancy.[1] It was estimated that cancer complicated 1 in every 1000 pregnancies, and the challenging case of cancer in pregnancy is becoming relatively more common.[2–4] This creates a unique and clinical dilemma as the diagnosis of cancer may be confounded by the overlapping symptoms of pregnancy, and the detection and treatment of cancer are also restricted.[5] Cancer not only affects the choice of treatment during pregnancy but also has a negative impact on the outcome of the mother and baby. It is one of the major causes of maternal death.[6] An Italian study containing 543 late maternal deaths from 2006 to 2012 reported that 38.8% of maternal deaths were caused by malignant neoplasms.[7] A national Reproductive Age Mortality Survey conducted in Norway also indicated that 60% of indirect maternal deaths are caused by malignant neoplasm.[8]

While most studies focused on the impact of cancer on the fetus, there is a paucity of studies investigating the risk of maternal deaths in cancer patients, and there is currently no literature on characteristics and risk factors for maternal deaths in women with cancers in details. Given that maternal deaths not only represent a family tragedy but also take a staggering toll on global public health, this analysis is important as it identifies the high-risk groups of maternal deaths among cancer patients, guiding for clinicians to develop risk-benefit counseling and shared decision-making process to reduce the risk of maternal deaths among cancer patients.

As such, to address the current lack of evidence, we conducted a population-based analysis of maternal death among cancer patients in a modern cohort from the surveillance, epidemiology, and end results (SEER) database. We aimed to characterize the risks of maternal deaths in cancer patients compared to the general population using a large population-based cohort.

2. Materials and methods

We extracted female patients with a cancer first diagnosed at ages 15 to 39 years between 2000 and 2016 (N = 240,561) from the SEER 18-registry database, which covers nearly 28% of the United States (US) population and collects cancer incidence and survival data.[9] Cases with a diagnosis solely from autopsy or without active follow-up were excluded. Available data about demographic characteristics from the SEER database included age at diagnosis, race, calendar year of diagnosis, and origin. Data on cancer type, treatment, follow-up time, and cause of death were also available. Patients with the cause of death coded as "complications of pregnancy, childbirth, and the puerperium" (A34, O00-O95, O98-O99 [ICD-10 codes]) were considered to have encountered maternal deaths.

Editor: Daryle Wane.

CY and ZY contributed equally to this article.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and analyzed during the current study are available in the SEER [https://seer.cancer.gov/].

[a] Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [b] Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [c] State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, China, [d] Department of Orthopedics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

[*] Correspondence: Bian Wu, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China (e-mail: bianwu@hust.edu.cn).

How to cite this article: Chen Y, Zheng Y, Yu K, Wu B. Maternal deaths among patients with cancer in the United States. Medicine 2021;100:46(e27922).

Received: 26 October 2020 / Received in final form: 2 November 2021 / Accepted: 6 November 2021

http://dx.doi.org/10.1097/MD.0000000000027922

As a comparison, we used mortality data of the general US population from the National Center for Health Statistics. The number of maternal deaths divided by person-years of survival was calculated as the mortality of maternal death. Among female cancer patients, standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) were calculated as previously described.[10,11] Briefly, SMRs were estimated as the ratios of observed maternal deaths in cancer patients to the expected number of maternal deaths in the general population with a similar distribution of age, race, and origin. A 5-year age range was used for standardization, and the 95% CI of SMR was determined using the Poisson distribution approximation. Cox proportional hazards models were fitted to perform multivariable modeling for factors associated with maternal deaths and to identify subgroups related to a higher risk of maternal deaths. A forest plot was also created to better present each prognostic factor's effect on maternal deaths. We calculated the hazard ratios (HRs) of different groups and determined them as the ratio of the mortality rate of the target group to the reference group. The 95% CI for SMRs and HRs were obtained based on a Poisson regression model. Observations were censored if patients did not die from maternal death at the time of the last follow-up. The survival time recorded as 0 month in the SEER database was converted to one-half of a month based on accepted epidemiologic practices.[12] The SEER data contains de-identified information and is freely available under a data use agreement with the National Cancer Institute. Thus, this study was considered to be exempt by the institutional review board of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. Informed consent was also waivered by the institutional review board since all SEER data was publicly available.

All statistical tests were 2-sided, and $P < .05$ was considered to be statistically significant. SEER*Stat 8.3.5 (seer.cancer.gov/seerstat/) and the R version 3.51 (www.r-project.org) were used for analysis.

3. Results

Among a total of 240,561 females with cancer at ages 15 to 39 years, 165 maternal deaths were observed, followed by 1,591,439 person–years (Table 1). The maternal death rate was 10.4/100,000 person–years and the SMR was 10.9 (95% CI, 9.36–12.7) compared with the general US population.

Of the deaths, 98 (59.4%) patients were in the age range of 30 to 39 years, 111 (67.3%) were white, 71 (43.0%) were in an advanced stage. 87 (52.7%) of patients underwent surgery and 97 (58.8%) received chemotherapy. Higher SMRs were observed in Hispanic (SMR, 21.4; 95% CI, 15.9–28.7), advanced stage (SMR, 83.7; 95% CI, 66.4–105.7), patients receiving chemotherapy (SMR, 20.4; 95% CI, 16.7–24.9), or not undergoing surgery (SMR, 28.6; 95% CI, 22.9–35.8).

The most common cancer types associated with maternal deaths were observed in cancers of breast 37 (22.4%), hematological 28 (17.0%), and digestive system 24 (14.5%). The SMR of maternal deaths was highest in cancers of the respiratory system (SMR, 124.91; 95% CI, 70.93–219.94), followed by cancers of the digestive system (SMR, 35.44; 95% CI, 23.75–52.88) and hematological malignancies (SMR, 20.35; 95% CI, 14.05–29.47). SMRs were the highest in the first month after a cancer diagnosis (SMR, 85.6; 95% CI, 53.9–135.9) and decreased gradually afterward.

In the multivariate analysis (Table 2), black race (hazard ratio [HR], 2.61; 95% CI, 1.74–3.93), Hispanic (HR, 1.57; 95% CI, 1.05–2.34), and advanced stage (HR, 6.93; 95% CI, 4.01–12.00) were associated with a higher risk of maternal deaths. Patients with cancer who received chemotherapy (HR, 1.59; 95% CI, 1.07–2.36) or who did not undergo surgery (HR, 1.59; 95% CI, 1.06–2.40) remained independent prognostic factors. A forest plot of HRs was also used to illustrate the risk factors associated with maternal deaths among patients with cancer (Fig. 1).

4. Discussion

Using data from the SEER database, we first found that the risk of maternal deaths among cancer patients was 10.9-fold that of the general US population. The risk of maternal deaths of cancer patients varies greatly by cancer type. Hispanic ethnic groups, advanced cancer stage, chemotherapy, non-surgery were risk factors associated with a higher risk of maternal deaths compared to the general US population. Black race, Hispanic, and advanced cancer stage were independent prognostic factors for maternal deaths among cancer patients.

Within the cancer cohort, the highest risk of maternal deaths was observed among patients with cancers of the respiratory system. First, this may be because patients with lung cancer are more likely to be delayed in diagnosis and treatment than patients with other tumors, leading to a higher risk of maternal deaths among patients with cancers of the respiratory system. Some nonspecific clinical manifestations of lung cancer, such as fatigue, dyspnea, and coughing, may be interpreted as the pregnancy itself, rather than tumor-related symptoms. Second, many patients worry about the effects of ionizing radiation and are reluctant to undergo imaging examinations during pregnancy. This also causes a delay in diagnosis. Third, respiratory malignancies, mainly gestational lung cancer, were usually diagnosed in advanced stages, with an aggressive behavior.[13] Mitrou et al[14] reported that more than 97% of the published cases of pregnant women with lung cancer were diagnosed with locally advanced or metastatic disease. In most cases, gestational lung cancer has poor chemotherapy effects and short overall survival, with the placenta and fetus involved by transmitted cancer cells. Further, patients with lung cancer or pregnancy-related death may have common risk factors such as smoking. Azim et al[15] found that 19 (61%) patients in their study of 31 gestational lung cancer cases had an active history of smoking. Smoking could increase the incidence of placental abruption and placenta previa,[16] which may cause bleeding, shock even maternal deaths.

We made a note that chemotherapy increased the risk of maternal deaths. This was a novel finding as few studies investigated the relationship between chemotherapy and maternal deaths. A Canadian survey of women diagnosed with bone and soft tissue tumors before and during pregnancy and a study on epithelial ovarian cancer indicated that considering the maternal mortality rate, chemotherapy must be evaluated for each woman on a case-by-case basis. However, the number of patients included in these studies was relatively small.[17,18] Therefore, the implication of chemotherapy to cancer patients complicated by pregnancy may be underappreciated, and whether chemotherapy would increase the risk of maternal deaths still requires more large-scale and in-depth population-based researches.

Table 1

Maternal deaths among female patients with cancer at ages 15 to 39 years between 2000 and 2016 by baseline characteristics.

			Maternal deaths				
			Patients with cancer (age: 15–39)		General population (age: 15–39)		
Characteristics	No. of patients with cancer (%)	Follow-up time in total	No. of observed deaths (%)	Mortality rate*	No. of expected deaths (%)	Mortality rate*	SMR (95% CI)†
All time	240,561 (100.0)	1,591,439	165 (100.0)	10.4	15.1	0.95	10.9 (9.36–12.7)
Age							
15–19	12,986 (5.4)	87,688	9 (5.5)	10.3	0.21	0.24	43.1 (22.4–82.8)
20–29	62,003 (25.8)	406,969	58 (35.2)	14.3	3.93	0.97	14.8 (11.4–19.1)
30–39	165,572 (68.8)	1,096,782	98 (59.4)	8.94	11.0	1.00	8.91 (7.31–10.9)
Race							
White	184,556 (76.7)	1,252,138	111 (67.3)	8.86	9.54	0.76	11.6 (9.66–14.0)
Black	26,788 (11.1)	164,558	42 (25.5)	25.5	4.11	2.50	10.2 (7.55–13.8)
Other	29,217 (12.1)	174,742	12 (7.3)	6.87	1.48	0.85	8.11 (4.61–14.3)
Year							
2000–2004	63,064 (26.2)	724,767	44 (26.7)	6.07	5.53	0.76	7.95 (5.92–10.7)
2005–2009	70,691 (29.4)	556,141	69 (41.8)	12.4	5.81	1.04	11.9 (9.38–15.0)
2010–2016	106,806 (44.4)	310,530	52 (31.5)	16.7	3.79	1.22	13.7 (10.5–18.0)
Origin							
Hispanic	45,827 (19.1)	255,761	44 (26.7)	17.2	2.06	0.81	21.4 (15.9–28.7)
NonHispanic	194,734 (80.9)	1,335,678	121 (73.3)	9.06	13.1	0.98	9.26 (7.75–11.1)
Stage							
In situ	21,252 (8.8)	179,421	0 (0.0)	0.00	1.58	0.88	NA
Localized	87,836 (36.5)	688,113	29 (17.6)	4.21	6.42	0.93	4.52 (3.14–6.50)
Regional	45,671 (19.0)	311,614	31 (18.8)	9.95	3.05	0.98	10.2 (7.16–14.5)
Advanced	21,052 (8.8)	86,013	71 (43.0)	82.5	0.85	0.99	83.7 (66.4–105.7)
Unstaged	64,750 (26.9)	326,278	34 (20.6)	10.4	3.24	0.99	10.5 (7.50–14.7)
Surgery							
Yes	186,725 (77.6)	1,320,745	87 (52.7)	6.59	12.4	0.94	7.04 (5.71–8.69)
No	51,622 (21.5)	259,519	76 (46.1)	29.3	2.66	1.02	28.6 (22.9–35.8)
Unknown	2,214 (0.9)	11,175	2 (1.2)	17.9	0.12	1.04	17.2 (4.30–68.7)
Chemotherapy							
Yes	80,341 (33.4)	476,206	97 (58.8)	20.4	4.75	1.00	20.4 (16.7–24.9)
No/unknown	160,220 (66.6)	1,115,233	68 (41.2)	6.10	10.4	0.93	6.55 (5.17–8.31)
Radiation							
Yes	66,885 (27.8)	449,671	44 (26.7)	9.78	4.33	0.96	10.2 (7.56–13.7)
No/unknown	173,676 (72.2)	1,141,768	121 (73.3)	10.6	10.8	0.95	11.2 (9.37–13.4)
Time from cancer diagnosis							
1 m	240,561 (100.0)	19,825	18 (10.9)	90.8	0.21	1.06	85.6 (53.9–135.9)
2–12 m	235,230 (97.8)	184,361	55 (33.3)	29.8	1.94	1.05	28.4 (21.8–36.9)
13–60 m	207,999 (86.5)	671,643	61 (37.0)	9.08	6.76	1.01	9.02 (7.02–11.6)
61–120 m	132,901 (55.2)	496,480	23 (13.9)	4.63	4.51	0.91	5.10 (3.39–7.68)
121+m	66,956 (27.8)	219,247	8 (4.8)	3.65	1.71	0.78	4.67 (2.33–9.33)
Type							
Breast	52,355 (21.8)	360,317	37 (22.4)	10.27	3.67	1.02	10.07 (7.3–13.9)
Hematological	23,321 (9.7)	152,994	28 (17.0)	18.30	1.38	0.90	20.35 (14.05–29.47)
Digestive system	13,721 (5.7)	64,973	24 (14.5)	37.0	0.68	1.04	35.44 (23.75–52.88)
Female genital system	37,415 (15.6)	258,439	20 (12.1)	7.74	2.42	0.93	8.28 (5.34–12.83)
Respiratory system	2650 (1.1)	10,172	12 (7.3)	118.0	0.10	0.94	124.91 (70.93–219.94)
Brain and other nervous system	14,235 (5.9)	81,015	11 (6.7)	13.58	0.78	0.97	14.03 (7.77–25.33)
Skin excluding basal and squamous	31,353 (13.0)	242,961	10 (6.1)	4.12	1.86	0.76	5.38 (2.9–10)
Endocrine system	49,258 (20.5)	321,540	6 (3.6)	1.87	2.99	0.93	2.01 (0.9–4.46)
Bones and soft tissue	4994 (2.1)	30,586	5 (3.0)	16.35	0.26	0.87	18.87 (7.85–45.33)
Urinary system	4246 (1.8)	26,955	4 (2.4)	14.84	0.27	0.99	15.03 (5.64–40.05)
Head and neck	3514 (1.5)	23,781	1 (0.6)	4.21	0.23	0.97	4.35 (0.61–30.87)
Other	3499 (1.5)	17,705	7 (4.2)	39.54	0.18	0.99	39.76 (18.96–83.4)

The observed number of deaths represents the total number of maternal deaths in patients with cancer recorded during the study period; the expected number represents the number of individuals who have maternal deaths in the general population with a similar distribution of age, race, and origin.

CI = confidence intervals, SMR = standardized mortality ratio.

* Per 100,000 person–years.

† The SMRs were estimated as the ratios of observed to expected number of deaths.

Table 2

Hazard ratios of maternal deaths among cancer patients.

	Unadjusted		Adjusted	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age				
15–19	0.75 (0.36–1.58)	.45	0.52 (0.24–1.11)	.092
20–29	Reference		Reference	
30–39	0.66 (0.47–0.94)	.021	0.68 (0.48–0.98)	.04
Race				
White	Reference		Reference	
Black	2.91 (2.01–4.21)	<.001	2.61 (1.74–3.93)	<.001
Other	0.70 (0.36–1.34)	.28	0.77 (0.40–1.49)	.44
Year				
2000–2004	Reference		Reference	
2005–2009	1.79 (1.18–2.71)	.006	1.40 (0.82–2.37)	.21
2010–2016	1.38 (0.87–2.20)	.17	0.92 (0.47–1.79)	.8
Origin				
Hispanic	1.74 (1.20–2.51)	.003	1.57 (1.05–2.34)	.028
NonHispanic	Reference		Reference	
Stage				
In situ	NA		NA	
Localized	Reference		Reference	
Regional	2.16 (1.30–3.60)	.003	1.73 (1.01–2.96)	.046
Distant	13.93 (8.93–21.71)	<.001	6.93 (4.01–12.00)	<.001
Unstaged	1.71 (1.00–2.90)	.048	1.07 (0.60–1.92)	.82
Surgery				
Yes	Reference		Reference	
No	3.49 (2.51–4.85)	<.001	1.59 (1.06–2.40)	.025
Unknown	2.61 (0.64–10.61)	.18	2.17 (0.53–8.92)	.282
Chemotherapy				
Yes	3.88 (2.77–5.43)	<.001	1.59 (1.07–2.36)	.021
No/unknown	Reference		Reference	
Radiation				
Yes	Reference		Reference	
No/unknown	0.93 (0.65–1.32)	.67	1.13 (0.77–1.64)	.53

CI = confidence intervals, HR = hazard ratio, NA = not applicable.

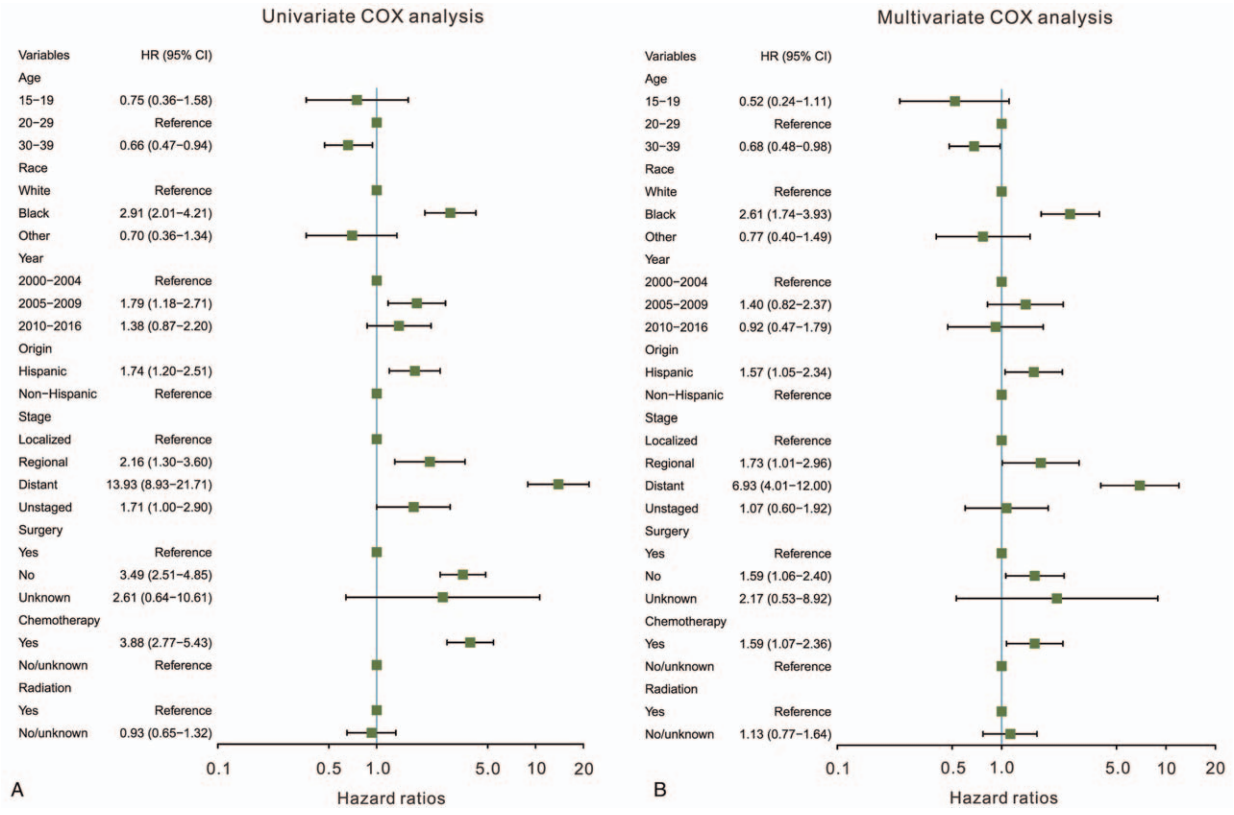

Figure 1. Forest plot of the risk factors associated with maternal deaths among patients with cancer. CI = confidence intervals, HR = hazard ratio.

The advanced stage was related to the highest risk of maternal deaths. Nearly half of all maternal deaths occurred in cancer patients in advanced stages. On one hand, since the symptoms and signs of these cancers were similar to the common complaints reported during pregnancy, pregnant women and clinicians may easily ignore them.[19] On the other hand, some mothers may avoid certain invasive examinations out of fear that the fetus would be exposed to radiation. We postulated that the altered hormonal environment of pregnancy may adversely influence the course of the cancer. In some cases, the increased circulation volume and cardiac output during pregnancy might predispose to rapid distant metastasis or advanced cancer stage. There was evidence that oncological surgery undertaken during pregnancy was well tolerated by mothers and fetuses. We also found that cancer patients undergoing surgery had a significantly lower risk of maternal deaths than non-surgical patients, suggesting that oncological surgery was a safe treatment for cancer patients with pregnancy.

Several limitations exist in our study. First, information regarding the proportion of patients with cancer complicating pregnancy and exact pregnant time were not available in the SEER database. Second, the details of the chemotherapy agents/regimens and radiotherapy doses could not be accessed due to the limitations of the SEER database itself, thus, we could not perform further analyses based on detailed treatment approaches. Third, due to the excessive reporting of maternal deaths in women ages > 40 years in the National Center for Health Statistics, patients over the age of 40 were excluded.

5. Conclusions

To conclude, we identified types of cancer and groups of patients associated with higher risks of maternal deaths. Our results call for women to have a thorough medical assessment before pregnancy and underscore the importance of appropriate risk assessment and management of cancer during pregnancy. A multidisciplinary approach should be utilized in all cases of malignancies in pregnancy.

Acknowledgments

We acknowledge the efforts of the National Cancer Institute and the SEER Program tumor registries in the creation of the SEER database and appreciated Haoran Xie from Huazhong University of Science and Technology for statistical consultation.

Author contributions

Conceptualization: Ying Chen, Yongqiang Zheng, Kaixu Yu, Bian Wu
Data curation: Yongqiang Zheng.
Formal analysis: Ying Chen, Yongqiang Zheng, Kaixu Yu.
Investigation: Ying Chen, Yongqiang Zheng, Kaixu Yu, Bian Wu.
Methodology: Ying Chen, Yongqiang Zheng.
Resources: Ying Chen.
Software: Kaixu Yu.
Supervision: Bian Wu.
Writing – original draft: Ying Chen, Yongqiang Zheng, Kaixu Yu, Bian Wu
Writing – review & editing: Ying Chen, Yongqiang Zheng, Bian Wu.

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