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Survival and medical costs of non-small cell lung cancer patients according to the first-line treatment: An observational study using the Kyoto City Integrated Database

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Abstract

Background: Lung cancer is the primary cause of cancer mortality and non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer cases. New drug treatments have been developed since 2010 but there are concerns about the increase in medical costs. This study aimed to compare survival and medical costs among patients with NSCLC according to their initial treatment to estimate the impact of early NSCLC detection.

Methods: Patients with primary NSCLC who filed insurance claims between April 2013 and March 2019 were identified using the Kyoto City Integrated Database. Patients were divided into two groups depending on their initial treatment: the resection group and drug or radiation group. The survival and medical costs were calculated.

Results: A total of 2609 patients with primary NSCLC were identified. Among them, 1035 patients underwent resection. The 5-year survival was 75% for the resection group while below 25% for the drug or radiation group. At 6 months of survival, the median cumulative total cost was 2409 thousand yen (interquartile range [IQR] 1947–4012 thousand yen) in the resection group and 2951 thousand yen (IQR 1600–4706 thousand yen) in the drug or radiation group. At 4 years of survival, the cumulative median total cost was 5257 thousand yen (IQR 3808–8243 thousand yen) in the resection group and 10 202 thousand yen (IQR 4845–20 450 thousand yen) in the drug or radiation group.

Conclusions: As a first-line therapy in newly diagnosed patients with NSCLC, surgical resection is associated with longer survival and lower medical costs than pharmacotherapy or radiotherapy.

KEYWORDS
administrative data, lung cancer, medical expenses, non-small cell

INTRODUCTION

Lung cancer is the primary cause of cancer mortality in many countries, and in 2020 was diagnosed in 2.2 million people worldwide, resulting in 1.8 million deaths.[1] In Japan, lung cancer was reported in 120 000 patients in 2017, and caused 75 000 deaths in 2019. In Japanese men and women combined, lung cancer is the third most frequently diagnosed cancer and the most common cause of death due to malignant neoplasms.[2] The age-adjusted annual incidence rates of lung cancer in Japan peaked in 2010 and decreased thereafter. However, the number of lung cancer patients continued to increase yearly up to 2018, partly because of population aging.[3] These statistics show that lung cancer is a major social challenge.

Lung cancers are often categorized into two histological subtypes: small cell lung cancers (SCLSs) and non-small cell lung cancers (NSCLCs). NSCLC accounts for approximately 85% of all lung cancer cases.[4,5] The treatment and prognosis of NSCLCs vary widely depending on the disease stage at diagnosis. Surgical resection is recommended for patients with tumor-node-metastasis (TNM) stage I and II lung cancers.[6,7] In surgical cases, the postoperative 5-year survival exceed 70%.[8] Surgery is not indicated for TNM stage 4 lung cancers, and patients with this stage of disease have a 5-year survival below 20%.[5] In addition, it is suggested that early lung cancer detection helps to reduce public healthcare expenditure.[9,10] Therefore, to extend survival and reduce the economic burden, it is important to detect lung cancers while they can be completely eradicated by resection.

Over the last 10 years, several molecularly targeted drugs and immune checkpoint inhibitors that effectively treat advanced NSCLCs have been discovered and approved for clinical use.[11,12] Although these new drugs have excellent therapeutic benefits, they are much more expensive than conventional pharmacotherapies, thereby increasing the public economic burden.[13] A high proportion of NSCLC patients are diagnosed with clinical stage 4 disease and they need pharmacotherapies. In the United States, 44% to 48% of new NSCLC cases between 2010 and 2017 were diagnosed at clinical stage 4.[14] In Japan, that clinical stage 4 accounted for 30%–33% of whole lung cancers in 2010–2013.[2] Cancer is a very costly medical condition in Japan, where its treatment accounted for 14.4% of the national healthcare costs in fiscal year 2018, a slight increase relative to fiscal year 2017.[15]

Kyoto City is one of the most populated Japanese local municipalities, with over 1 million residents. It has developed its own administrative database that contains information on public health insurance, medical services, and other resident data. Using a dataset containing all lung cancer patients who were treated between April 2013 and March 2019, we previously reported that during this period, 2-year survival improved, the proportion of patients who received surgery as first-line therapy increased, and healthcare costs increased due to a large rise in the cost of drugs.[16] In this study, we identified patients in the database who were newly diagnosed with NSCLC and divided them into two major groups by their initial treatment: surgical resection versus drug treatment or radiotherapy. We describe their survival and medical costs to assess the healthcare impacts of early NSCLC detection.

METHODS

Study design, population, and settings

This was an observational study that used data taken from the Kyoto City Integrated Database (KCIDB), a large-scale administrative database developed and maintained by the Kyoto City local government. Kyoto City is the eighth most populated city in Japan, with approximately 1.5 million people.[17]

The KCIDB covers National Health Insurance, Long-Term Care Insurance, and Advanced Elderly Medical Service Systems; annual lifestyle-related health checkups; and a resident register (deaths and moving into and out of the city). The National Health Insurance system covers self-employed and retirees and their family members. The Advanced Elderly Medical Service System covers 75 years old or older, and 65–74 years old with certain disabilities. The details of the KCIDB have been described elsewhere.[16] The health-related KCIDB data covers approximately 35% of Kyoto City residents. All KCIDB entries were de-identified and assigned new anonymous personal identifiers by the local government to link data entered into different systems. This study included data entered between April 2013 and March 2019.

The target disease of this study was newly diagnosed primary NSCLC, and study patients were identified as described below. First, health insurance claim data bearing the International Classification of Diseases 10th revision (ICD10) diagnostic code C33 (malignant neoplasm of trachea) or C34 (malignant neoplasm of bronchus and lung) were extracted, and their disease descriptions were checked using the treatment based algorithm explained below. Since the diagnostic codes used in health insurance claims are sometimes of limited medical accuracy, they should be combined with medical treatment data to improve their quality for use in scientific research.[18–20] The scope of lung cancer medical treatment was determined by consensus of a pulmonary internist (Daisuke Kobayashi [DK]) and a pharmacist (Yukiko Tateyama), and included surgery, pharmacotherapy, and radiotherapy (Tables S1–S3). When one or more of these modalities were recorded in the database along with lung cancer, they were considered to be lung cancer treatments. Using disease names as the sole criterion for a diagnosis of lung cancer could result in insufficient removal of SCLC patients from the study population. Therefore, patients who received drugs primarily targeting SCLCs (i.e., irinotecan, etoposide, nogitecan, and amrubicin) as first-line therapy were considered to have SCLCs and were excluded from the study population. Moreover, to exclude patients who were receiving lung cancer treatment before the start of the study period, individuals were removed if their lung cancer insurance claims were filed (i) between April 1 and September 30, 2013, or (ii) within 6 months of moving to Kyoto City. Patients whose lung cancer insurance claims were filed (iii) within 6 months of participating in the Advanced Elderly Medical Service System, with no available health insurance records before this participation, were also excluded because it was not definitively clear that these claims represented their initial treatment. Furthermore, to ensure a minimum of 2 years of follow-up, patients whose first lung cancer insurance claims were filed after March 31, 2017, were excluded.

This study was reviewed and approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (R3107). Informed consent was waived for this study because it was based on anonymized data and involved no personally identifiable information.

Data collection and quality control

For each patient, the date when their first lung cancer insurance claims were filed was defined as the index date, and data on their age and sex on this date were collected. When the index date did not include the day of the month, it was imputed to the first day of the month to determine patient age. Data on comorbid conditions were collected based on the ICD10 codes in the health insurance claims filed within 6 months of the index date. Comorbid conditions were adopted by consensus of two internists (Taku Iwami and DK, Table S4). Comorbidities in cases in which the disease name was indicated as "suspected" were excluded from the definition. Information on the status of certification of the need for long-term care or support under the Long-Term Care Insurance System was collected based on the most recent certification made within 6 months before the index date. The Long-Term Care Insurance System categorizes the levels of care services depending on the need for assistance with activities of daily life: 25 to <32 min (Level 1 Need for Support), 32 to <50 min (Level 2 Need for Support or Level 1 need for care. It depends on evaluation as clinical condition of causal diseases and dementia at the assessment conference), 50 to <70 min (Level 2 need for care), 70 to <90 min (Level 3 need for care), 90 to <110 min (Level 4 need for care), and ≥ 110 min (Level 5 need for care).[21,22] Data on patients vital and residential status as of March 2019 were taken from the resident register. Because the resident register provided information on year and month only, all death or dropout dates were calculated as occurring on the first day of the month.

Statistical analysis

Patients were divided into two groups depending on their initial treatment: resection versus drug treatment or radiotherapy. Numerical data were summarized using mean and standard deviation (SD). Categorical data were summarized using proportions. Patient background data included age,

TABLE 1 Patient characteristics by initial treatment

Variables	Resection $n = 1035$	Drug or radiation $n = 1574$
Age, average (SD)	73 (7.2)	74 (8.6)
75 years and over, n (%)	494 (47.7)	837 (53.2)
Male, n (%)	570 (55.1)	1052 (66.8)
Comorbidity, n (%)		
Chronic lung disease	429 (41.4)	597 (37.9)
Congestive heart failure	220 (21.3)	381 (24.2)
Cerebrovascular disease	162 (15.7)	250 (15.9)
Renal dysfunction	50 (4.8)	96 (6.1)
Hepatic dysfunction	81 (7.8)	112 (7.1)
Dementia	7 (0.7)	32 (2.0)
Needing long-term care, n (%)	105 (10.1)	296 (18.8)
Need support	69 (6.7)	106 (6.7)
Level 1	12 (1.2)	60 (3.8)
Level 2	15 (1.4)	72 (3.8)
Level 3	3 (0.3)	31 (4.6)
Level 4	5 (0.5)	18 (2.9)
Level 5	1 (0.1)	9 (1.1)

Abbreviation: SD, standard deviation.

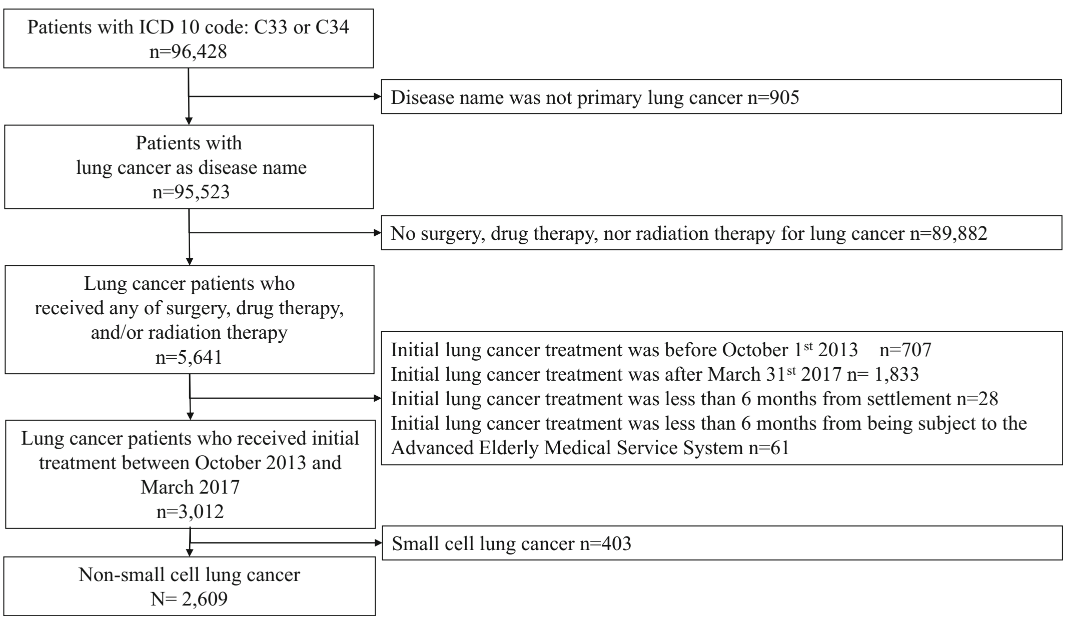

FIGURE 1 Patient flow diagram. ICD-10, International Classification of Diseases, Tenth revision

sex, and comorbid conditions. The status of the need for long-term care was defined whether or not they are certified as any level of need for support or care and the six classifications (Need Support and Level 1 to Level 5 Need for Care). Kaplan–Meier curves according to initial treatment were constructed to visualize survival times. Survival time was calculated as the difference between the index date and the date of death or drop out or the end of the observation (March 31, 2019). A total of 26 cases with the difference below 0 days were excluded from this analysis as wrong entries.

Total healthcare, hospitalization, and outpatient costs from the start of the initial treatment were computed for individual patients following periods: 6 months and 1, 2, 3, 4, and 5 years. To minimize the possibility of multidisciplinary terminal care interventions that would increase healthcare costs, these costs were calculated for patients who survived for longer than each periods.

Descriptive statistics were determined using SQL Server Management Studio, version 15.0 (Microsoft Corporation), and survival curves were plotted using Stata/MP, version 17 (StataCorp LLC).

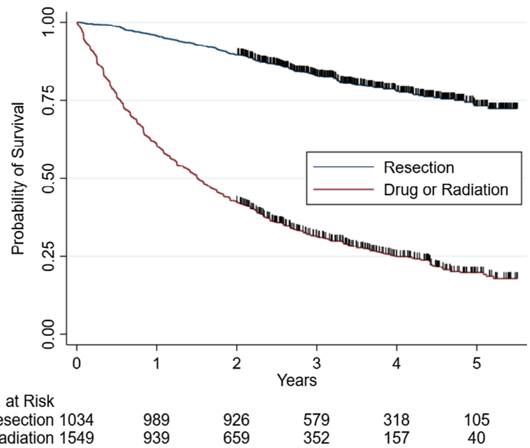

FIGURE 2 Kaplan–Meier survival curves of the initial treatment for non-small cell lung cancer (NSCLC).

RESULTS

During the study period, health insurance claims were filed for 724 928 patients, including 96 428 with ICD10 code C33 or C34. Of these patients, 905 treated for diseases other than lung cancer were excluded. Removal of patients with no records of medical treatment for lung cancer resulted in 5641 patients. The following patients were also then excluded: 707 and 1833 patients whose initial treatment took place before September 2013 and after April 2017, respectively; 28 patients whose index date was within 6 months of moving to Kyoto City; and 61 patients whose index date fell within 6 months of turning 75 years and who had no records of health insurance claims filed before age 75 years. Among the remaining 3012 patients, 403 were judged to have SCLCs. Finally, 2609 patients were included in the study population (Figure 1).

Patient backgrounds are summarized for the resection and the drug or radiation groups in Table 1. The mean age was 73 years (SD 7.2) in the resection group and 74 years (SD 8.6) in the drug or radiation group. Men accounted for 55.1% of the resection group and 66.8% of the drug or radiation group. No noteworthy differences were noted between groups in the distribution of comorbid conditions. In the resection and drug or radiation groups, 10.1 and 18.8% of the patients, respectively, were certified as needing long-term care before they were diagnosed with lung cancer.

TABLE 2 Cumulative cost of survivor healthcare by survival time from initial lung cancer treatment

Variables, 1000¥, median, (IQR) Total	6 month $n = 2218$	1 year $n = 1937$	2 year $n = 1587$	3 year $n = 931$	4 year $n = 481$	5 year $n = 154$
Total cost	2566 (1947–4012)	3262 (2349–5486)	4485 (2888–7732)	5387 (3524–9607)	6150 (4124–11 383)	5813 (4256–11 130)
Hospitalization cost	1952 (1455–2844)	2050 (1604–3345)	2287 (1718–4100)	2570 (1790–4400)	2624 (1816–4914)	2408 (1753–4453)
Outpatient cost	586 (311–1180)	983 (574–1923)	915 (387–2136)	2280 (1434–4501)	2818 (1817–5787)	3292 (2167–5209)
Resection	$n = 1020$	$n = 989$	$n = 926$	$n = 579$	$n = 318$	$n = 108$
Total cost	2409 (2064–3224)	2858 (2346–4072)	3802 (2792–5736)	4710 (3328–7052)	5257 (3808–8243)	5659 (4283–8643)
Hospitalization cost	1988 (1732–2614)	2033 (1765–2933)	2165 (1806–3619)	2457 (1856–3934)	2615 (1876–4287)	2475 (1855–4334)
Outpatient cost	356 (226–549)	661 (458–999)	800 (336–1583)	1915 (1211–2788)	2535 (1566–3604)	3079 (1884–4336)
Drug or radiation	$n = 1198$	$n = 948$	$n = 661$	$n = 352$	$n = 163$	$n = 46$
Total cost	2951 (1600–4706)	4160 (2377–6932)	6207 (3441–11 191)	8315 (4331–16 274)	10 202 (4845–20 450)	8713 (4233–19 170)
Hospitalization cost	1831 (969–3148)	2129 (1049–3894)	2692 (1261–4970)	2868 (1266–5432)	2856 (1269–5994)	1947 (699–5756)
Outpatient cost	1001 (570–1823)	1636 (987–3399)	1184 (498–3915)	4038 (1971–11 326)	5573 (2551–14 650)	5164 (2795–14 927)

The Kaplan–Meier survival curves of the resection and drug or radiation groups are shown in Figure 2.

These curves markedly differed from each other, starting immediately after the initial treatment. The 5-year survival was 75% for the resection group and below 25% for the drug or radiation group.

Cumulative medical costs of the resection and drug or radiation groups are summarized for different survival periods in Table 2. At 6 months of survival, the median total cost was 2409 thousand yen (interquartile range [IQR] 2064–3224 thousand yen) in the resection group and 2951 thousand yen (IQR 1600–4706 thousand yen) in the drug or radiation group. The estimates for hospitalization and outpatient costs were also lower for the resection group, with a median difference of approximately 5000 thousand yen for both costs. At 4 years of survival, the median total cost was 5257 thousand yen (IQR 3808–8243 thousand yen) in the resection group and 10 202 thousand yen (IQR 4845–20 450 thousand yen) in the drug or radiation group. In the drug or radiation group, the total medical cost at 4 years of survival was markedly higher than at 6 months of survival. The difference between groups in total medical cost continued to increase until 4 years after initial treatment, at which point the total medical cost of the drug or radiation group was approximately 1.9 times higher than that of the resection group.

DISCUSSION

Using an administrative healthcare database, we identified 2609 newly diagnosed NSCLC patients and clearly demonstrated that the resection group had longer survival and lower medical costs than the drug or radiation group. The results of this study from the metropolitan area in Japan where the super-aging society is developing rapidly underscore the medical and health economic significance of early lung cancer detection.

Using approaches similar to the present study, researchers in Spain[23] and South Korea[24] evaluated the impacts of lung cancer treatment on survival and medical expenditures. In the Spanish study, the 30-month mortality rates were 79.3 and 24.4% for medically and surgically treated patients, respectively. The mean medical cost required in the 2.5 years after diagnosis was 36% lower in surgically treated patients (€13 172) than in medically treated patients.[23] In the South Korean study, the estimated survival times during 120 months of follow-up were 7.8 years for the surgery group and 2.8 years for the chemotherapy and/or radiotherapy group. The surgery group was associated with the highest medical expenditure in the first year after diagnosis, although the estimated overall mean annual cost decreased in the following order: chemotherapy and/or radiotherapy; surgery plus chemotherapy and/or radiotherapy; and surgery.[24] In our study, the mean age in the resection group was 73 years and in the drug or radiation group was 74 years. Because of the characteristics of DB, patients in our study were older than in previous studies (77.8% of the surgery group and 60.2% of the medically treated group were under 75 years in the Spanish study; 63.7 and 65.8 years, respectively, in the surgery only group and chemo and/or radiotherapy group in the Korean study). However, the results of both studies showed similar trends to those of the present study, suggesting that the results are somewhat consistent across regions, health care systems, and ages. In particular, our study demonstrated the benefit of surgery, even in the context of a relatively high average age of 70s based on real world data. In a situation where aging is progressing worldwide, it is important. In terms of survival, both studies showed increased mortality in the drug or radiation group immediately after treatment or diagnosis. Compared to surgical treatment, which targets early-stage cancers, the drug or radiation group targets advanced cancers. Also, poor general health is not an indication for surgery.[6,7] In both the present and two previous studies, age tended to be younger in the surgical group. In addition, in Spain and in our study, the rate of comorbidity was higher in the drug or radiation group and the general condition of patients was relatively poor. These combined factors may be associated with earlier mortality. In both these and the present study, all lung cancer patients required the medical cost year by year, but the medical cost of the surgery group became lower than that of the other groups as patients survived longer. This may be because successful surgical resection in patients eliminates the need for additional costly treatments, whereas radiotherapy and pharmacotherapy often require major follow-up treatments. In addition, patients who do not undergo surgical resection may need relatively more treatment for disease other than cancer. As mentioned earlier, they have many comorbidities and a relatively poor general health, which may be a situation in which they are continually incurring treatment costs other than for lung cancer. This study suggests surgery remains the best practice in the treatment of NSCLC even in a period when new and effective pharmacotherapies for NSCLC improved dramatically. Adaptation of surgical management for lung cancer is based on early detection. Therefore, it is important to establish and validate screening or other methods for early detection. Future studies are warranted to evaluate the effectiveness of screening to early detection of lung cancer.

Our study had several limitations. Under the Japanese healthcare program, corporate employees and their dependent family members are covered by the Employee Health Insurance System, and self-employed and nonemployed individuals and their dependent family members are covered by the National Health Insurance System. The KCIDB includes data from the latter system, but has no access to the former. Although the KCIDB provides healthcare data of individuals aged 75 years or older who are covered by the Advanced Elderly Medical Service System, it does not contain information on their past health insurance claims made under the Employee Health Insurance System. We addressed this problem by defining elimination criterion (iii), as explained in the Methods section. Of note, the vital status data used in this study were taken from the official resident registry, and had excellent reliability. Given the nature and characteristics of the individuals included in the KCIDB, we should use caution when generalizing the findings of this study. However, findings on advanced elderly people may be generalizable because almost all the Kyoto City residents aged 75 years or older are covered by the KCIDB. Because the KCIDB hosts administrative data, attention must be exercised when using the KCIDB data for scientific analysis. The accuracy of the diagnostic codes entered in the database should be carefully scrutinized. As far as this study is concerned, disease misclassification risks were minimal since the data reflected actual health insurance claims filed under the national health program. Another disadvantage of using the KCIDB for medical research is that it does not provide information on the pathological characteristics or stages of lung cancer. As shown in previous studies, cancer stage affects medical costs and survival,[5,25] even among patients who receive the same treatment. In a future study we will investigate the relationship between disease stage and outcomes by linking the KCIDB and the National Cancer Registry.

In conclusion, as a first-line therapy in newly diagnosed NSCLC patients, surgical resection is associated with longer survival and lower medical costs than pharmacotherapy or radiotherapy. These clinical and economic benefits will be enhanced by promoting early detection of NSCLC and thereby increasing the opportunities for definitive surgical resection.

AUTHOR CONTRIBUTIONS

Design: TS, Y Tateyama, DK, KY, Y Takahashi, TI. Data acquisition: Y Takahashi, TN, TI. Statistical analysis and interpretation: TS, Y Tateyama. DK, KY, Y Takahashi, HU, KS, TI. Manuscript writing: TS, Y Tateyama, DK, TI. Approval of the final text: All authors.

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Kyoto City have participated in the data collection, study design, analysis, and preparation of the manuscript. This study was supported by the Japan Society for the Promotion of Science KAKENHI (20H01594), a joint research grant from Healthtech Laboratory Inc., and Kyoto University and a joint research grant from Healthtech Laboratory Inc., and Astrazeneca. K.K. Healthtech Laboratory Inc., and AstraZeneca K.K. participated in constructing the concept of study design, analysis, and manuscript.

CONFLICT OF INTEREST STATEMENT

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Drs Shimamoto and Tateayam are employed by the Kyoto University and Health Tech Laboratory Inc., Joint Research Fund.

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DATA AVAILABILITY STATEMENT

The data of this study are available from Kyoto City but restrictions access to these data, which were used under contract for the current study and so are not publicly available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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