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Evaluating treatment strategies for non–small cell lung cancer during COVID-19

A propensity score matching analysis

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Abstract

We employed pandemic treatment strategies that we developed at the beginning of the coronavirus disease 2019 (COVID-19) pandemic, and it was not clear whether any adverse results were associated with our strategies. Therefore, we carried out a retrospective study to compare our pandemic treatment strategies with prepandemic protocols to determine whether the strategies used during the high-risk period of COVID-19 were appropriate. The observation period was September 2019 to February 2020. Patients hospitalized from December 2019 to February 2020 were included as an experimental group, and individuals hospitalized from September 2019 to November 2019 were included as a control group. All non–small cell lung cancer patients hospitalized during the observation period were included except for pediatric and obstetric patients, patients younger than 18 years old, and patients admitted only for routine follow-up examinations. Treatment strategies were evaluated based on the prognosis of the different treatment methods, including surgical and nonsurgical treatments and discontinuation of therapy. Survival curves were analyzed using the Kaplan–Meier method. Cox regression analysis was used for multivariate analysis of risk factors for progress-free survival. Propensity score matching was used for clinical characteristics to adjust for selection bias. Therapy discontinuation in the experimental group was significantly higher than in the control group ($P < .001$). The differences in cancer progression and the number of deaths between the 2 groups were not significant ($P = .38$ and .13, respectively). For late-stage patients, there were significant differences in nonsurgical treatment and discontinued therapy ($P < .001$ and $< .001$, respectively) between the 2 groups, while the cancer progression and death toll differences were not significant ($P = .20$ and .20, respectively). For early-stage patients, the differences in surgical treatment, discontinued therapy, cancer progression, and death toll were not significant ($P = .24$, 0.24, 0.61, and 0.49, respectively) between the 2 groups. Multivariate analysis revealed that temporary discontinuation of therapy did not predict poor progress-free survival independently (hazard ratio = 1.007, 95% confidence interval: 0.653–1.552, $P = .98$). For patients in geographical regions with a high risk for COVID-19 infections, temporarily suspending treatment for late-stage non–small cell lung cancer patients is not likely to significantly impact their prognosis if they can return to treatment within 3 months of discontinuation.

Abbreviations: AAH = atypical adenomatous hyperplasia, ADC = adenocarcinoma, Ais = adenocarcinoma in situ, CI = confidence interval, COPD = chronic obstructive pulmonary disease, CSCO = Chinese Society of Clinical Oncology, ESMO = European Society of Medical Oncology, GGN = ground-glass nodule, HR = hazard ratio, LSOL = space-occupying lesion, NICE = National Institute for Health and Care Excellence, NSCLC = non–small cell lung cancer, PFS = progress-free survival, PSM = Propensity scores matching, SCC = squamous cell carcinoma.

Keywords: COVID-19, non–small cell lung cancer, prognosis, therapy discontinuance

1. Introduction

The Wuhan Municipal Health Commission first reported the existence of coronavirus disease 2019 (COVID-19) on December 8, 2019, and subsequently confirmed that it emerged as early as December 1, 2019.[1] Since the outbreak of COVID-19, the Chinese government has executed comprehensive testing methods, including chest computed tomography (CT) imaging and viral nucleic acid detection.[2,3] When carrying out a chest CT scan, the physician may unexpectedly discover the presence of lung space-occupying lesions (LSOLs), including ground-glass nodules, solid nodules, and partially

MY and YC contributed to the work equally.

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solid nodules or pulmonary masses, which may be a symptom of lung cancer.

Cancer patients constitute a specific subgroup of patients in this pandemic due to their typically advanced age, complex health conditions, and low immune function, which increase the risk of adverse and more severe consequences resulting from COVID-19 infection.[4] For cancer patients undergoing active treatment or continued observation, lymphopenia, an independent indicator for a poor prognosis in COVID-19 patients, is common, and the immune response is impaired in cancer patients.[5,6] Thus, cancer patients exhibit a higher mortality rate compared to the general population. Rogado et al[7] reported a significant increase in the mortality rate in lung cancer patients with COVID-19 compared to all COVID-19 patients, which may be due to a greater predisposition to respiratory infections and a previous diagnosis of chronic obstructive pulmonary disease (COPD) or metastatic disease in lung cancer patients. Therefore, providing care to patients with non–small cell lung cancer (NSCLC) has been challenging in this pandemic.[8]

Before the pandemic, we adopted treatment strategies following the Chinese Society of Clinical Oncology guidelines, which recommended surgical treatment for patients in stages I and II and resectable stages IIIA and IIIB. Nonsurgical treatments were recommended for postoperative, locally advanced NSCLC patients and patients not suitable for surgical treatment. However, because few guidelines were available at the beginning of the pandemic, we primarily used a surgical treatment strategy for early-stage NSCLC patients and nonsurgical treatment and discontinuation of therapy strategies for patients in late-stage NSCLC. These strategies were employed at the beginning of the pandemic because, in our opinion, early-stage NSCLC patients exhibited less respiratory disease and trauma during surgery. Therefore, it was thought that these patients could recover from COVID-19 and be discharged more quickly. Also, late-stage NSCLC patients routinely exhibited complex health conditions and low immune function that often led to complications, including longer in-hospital stays and increased risk of infection.

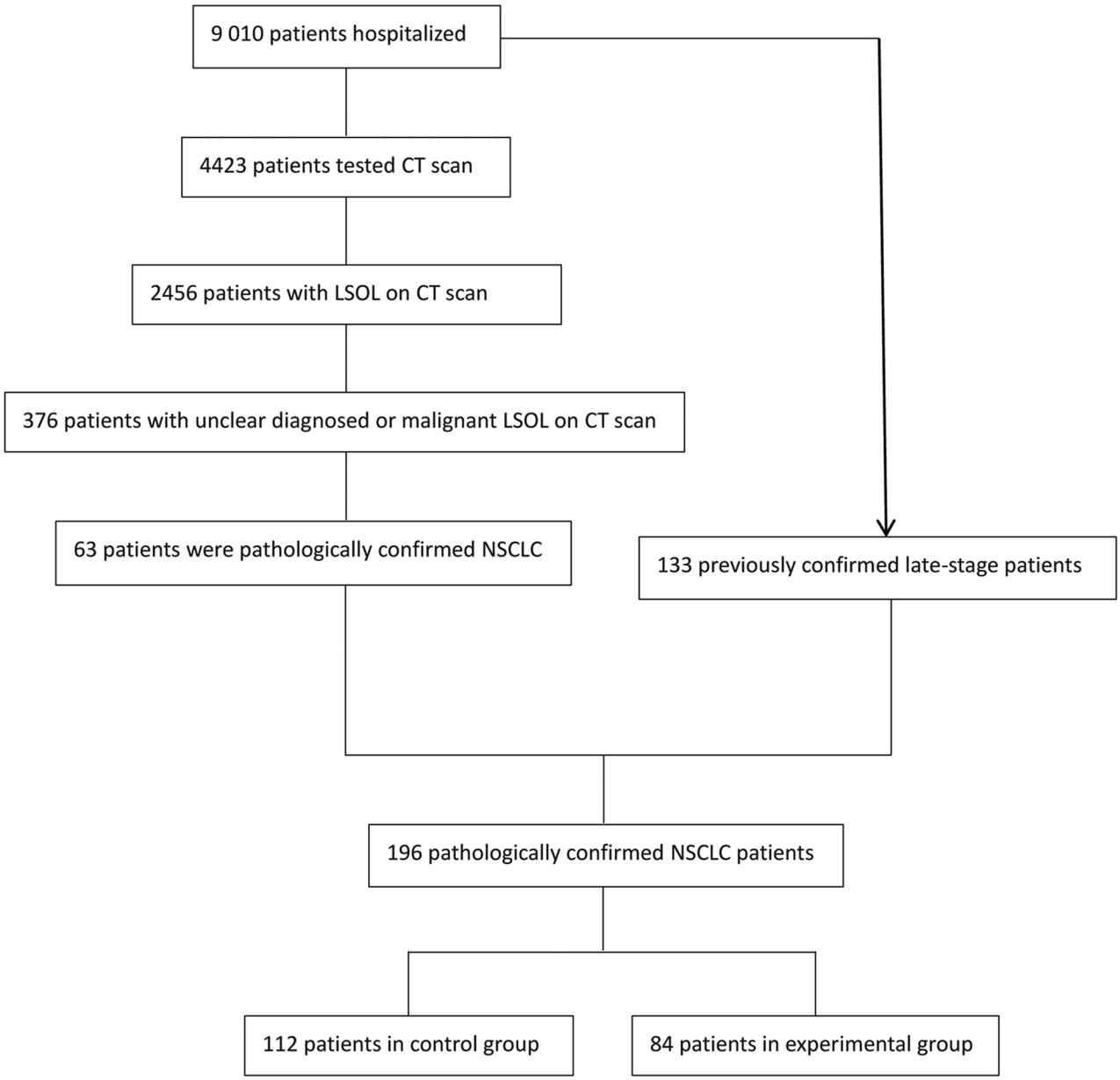

Figure 1. The flowchart of diagraming the patient selection process. CT = computed tomography, LSOL = space-occupying lesion, NSCLC = non–small cell lung cancer.

As the pandemic progressed, many guidelines were proposed to manage this vulnerable patient population. Kumar et al[9] suggested that in the case of limited surgical resources or high risks associated with perioperative care, NSCLC patients who presented with advanced yet localized disease that was resectable could be treated with specific, nonsurgical management, including chemotherapy, chemoimmunotherapy, radiation therapy, and immunotherapy. A previous consensus statement suggested that during the COVID-19 pandemic, the annual screening exam and treatment of clinical stage I NSCLC should be delayed.[10] The statement also concluded that it could be acceptable to delay the surveillance CT scan for approximately 3 to 6 months for patients with an incidentally detected pure ground-glass nodule of any size, a partially solid lung nodule with a solid component of 6 to 8 mm, or a solid nodule that was <8 mm in diameter.[10] Raskin et al[11] recommended delaying surgery for up to 3 months in cases of small-size NSCLC that did not appear to grow rapidly, and the growth rate should be followed utilizing chest CT scans.

These guidelines were opposite to our pandemic treatment strategies mentioned above, and we adjusted our strategy according to the recommended guidelines. However, as some regions of the country started transitioning to become areas at low risk for COVID-19 infections and more people have recognized the pandemic will not end soon, some of these guidelines might not be appropriate in certain situations. For example, if the pandemic continues for years, it seems ill-advised to transiently delay annual screening exams, treatment for early-stage NSCLC, and postpone surveillance CT scans for months. From this perspective, our initial pandemic treatment strategies appeared to present only limited feasibility. Therefore, we carried out a retrospective study to compare our pandemic treatment strategies with prepandemic strategies to determine whether our initial treatment strategies during the high-risk period of COVID-19 were reasonable.

2. Methods

2.1. Observation period

Our treatment strategies during the pandemic included 3 stages. The first stage was the high-risk period from December 2019 to February 2020, when few guidelines existed, and we developed our own pandemic treatment strategies. The second stage also occurred in the high-risk period, but by this time, numerous guidelines had been proposed, and we adjusted our treatment strategies to follow these guidelines. The third stage was during a period of low to no risk, and the treatment strategies were in accordance with prepandemic strategies. The aim of this study was to determine the applicability of our initial pandemic treatment strategies during the high-risk period of COVID-19 infection. We chose patients hospitalized from December 2019 to February 2020 as the experimental group and individuals hospitalized in a period of equal time before the pandemic, from September 2019 to November 2019, as the control group.

Table 1

Clinical characteristics of the 9010 hospitalized patients.

Items	Control group (n = 4764)	Experimental group (n = 4246)	*P* valve
Sex			
Male	2364 (26.24%)	2154 (23.91%)	.30
Female	2400 (26.64)	2092 (23.22%)	
Age (yr)	60.85 ± 17.65	61.49 ± 17.40	.08
Patients test CT scan	1694 (18.80%)	2729 (30.29%)	<.001
Total LSOLs	713 (7.91%)	1743 (19.35%)	<.001
Unclear diagnosis LSOLs	77 (0.85%)	174 (1.93%)	<.001
Malignant LSOLs	49 (0.54%)	76 (0.84%)	<.001

CT = computed tomography, LSOL = lung space-occupying lesion, NSCLC = non–small cell lung cancer.

2.2. Patients

All NSCLC patients hospitalized during the observation period were included, except for pediatric and obstetric patients, patients younger than 18 years old, and patients admitted only for routine follow-up examinations. Individuals were included in the control group if the date of their initial hospitalization was during the control period, and they followed their medication protocol throughout the entire observation period without changing treatment methods. However, when evaluating the treatment strategy, if a patient experienced neoadjuvant therapy during the control period but underwent surgery during the experimental period, or continued treatment during the control period and discontinued the treatment during the experimental period, that individual was included in the experimental group. This protocol was used because, on the one hand, surgery is the primary treatment protocol for resectable NSCLC, even if previous neoadjuvant therapy is used. On the other hand, discontinuation of therapy can result in serious adverse outcomes for cancer patients and even negate previous efforts. Therefore, the period when surgery was performed or therapy was discontinued was the target period. However, if a patient started adjuvant therapy during or before the control period and finished the therapy during the entire observation period, underwent surgery, or discontinued treatment during the control period, the patient was placed in the control group.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Sichuan Science City Hospital (no. 2020007), and informed consent for this retrospective analysis was obtained from all patients or their legal guardians for the purpose of publication.

2.3. Treatment strategy

Any patient with an unclear diagnosis or a malignant LSOL discovered on CT was encouraged to undergo a definitive diagnosis through biopsy with permission from the patient or their family members. The treatment strategies in the control group followed the Chinese Society of Clinical Oncology guidelines. We chose patients in stages I and II and resectable stages IIIA and

Table 2

Clinical characteristics of the 63 newly confirmed NSCLC patients.

Items	Control group (n = 24)	Experimental group (n = 39)	*P* value
Sex			
Male	10 (15.87%)	19 (30.16%)	.61
Female	14 (22.22%)	20 (31.75%)	
Age (yr)	65.46 ± 11.10	61.67 ± 13.40	.25
Tumor types			
AAH	1 (1.59%)	1 (1.59%)	
Ais	1 (1.59%)	1 (1.59%)	.84
ADC	19 (30.16%)	29 (46.03%)	
SCC	3 (4.76%)	8 (12.70%)	
Stage			
AAH	1 (1.59%)	1 (1.59%)	
Ais	1 (1.59%)	1 (1.59%)	
I	13 (20.63%)	29 (46.03%)	.44
II	8 (12.70%)	8 (12.70%)	
III	0 (0%)	0 (0%)	
IV	1 (1.59%)	0 (0%)	

AAH = atypical adenomatous hyperplasia, ADC = adenocarcinoma, Ais = adenocarcinoma in situ, NSCLC = non–small cell lung cancer, SCC = squamous cell carcinoma.

IIIB for surgical treatment. Nonsurgical treatments, including chemotherapy, targeted therapy, radiation therapy, and immunotherapy, were performed for postoperative, locally advanced NSCLC patients and patients not suitable for surgical treatment.

At the beginning of the pandemic, we developed our own treatment strategies. In the experimental group, patients in stages I and II were advised to undergo surgery. In contrast, patients in stages III and IV were advised to delay any therapy for 3 months, including surgery, chemotherapy, radiation therapy, and immunotherapy. However, targeted therapy was not delayed because it occurred at outpatient locations. There were 2 principles underlying the discontinuation of therapy, including a doctor's suggestion and patient-associated considerations. Doctors primarily suggested that patients who were in late stages temporarily delay therapy. Patient factors included those who refused treatment and tentatively discontinued therapy due to physical weakness, toxicity, or other side effects. All patients treated during the pandemic underwent a chest CT scan and a respiratory virus nucleic acid test for COVID-19. All treatments were suspended if a patient was suspected to be infected.

2.4. Treatment strategy evaluation

Treatment strategies were evaluated based on the prognosis of the different treatment methods, including surgical and nonsurgical treatments and discontinued therapies. If a patient stopped therapy for >1 month, they were considered to have discontinued therapy. The prognosis was classified into 3 levels: stable, progression, and death. Stable disease was defined as no recurrence or metastasis present. Progression was designated when any sign or symptom of recurrence was present, or metastasis and tumor growth were discovered during reexamination. Patients in early-stage NSCLC included atypical adenomatous hyperplasia, adenocarcinoma in situ, and stages I and II. Late-stage patients included stages III and IV. We followed up with patients via medical records and telephone interviews, and the deadline was April 2021.

Table 3

Clinical characteristics of the 196 NSCLC patients pre- and post-PSM.

	Pre-PSM			Post-PSM		
Items	**Control group (n = 112)**	**Experimental group (n = 84)**	***P* value**	**Control group (n = 67)**	**Experimental group (n = 67)**	***P* value**
Sex			0.77			.23
Male	66 (33.67%)	47 (23.98%)		32 (23.89%)	40 (29.85%)	
Female	46 (23.47%)	37 (18.88%)		35 (23.12%)	27 (20.15%)	
Age (yr)	65.68 ± 10.51	63.45 ± 11.66	.16	65.21 ± 10.87	64.84 ± 11.06	.80
Tumor types			.97			.51
AAH	1 (0.51%)	1 (0.51%)		1 (0.75%)	0 (0%)	
Ais	1 (0.51%)	1 (0.51%)		1 (0.75%)	1 (0.75%)	
ADC	93 (47.45%)	71 (36.22%)		15 (11.20%)	10 (7.46%)	
SCC	17 (8.67%)	11 (5.61%)		50 (37.31%)	56 (41.79%)	
Stage			.004			.86
AAH	1 (0.51%)	1 (0.51%)		1 (0.75%)	0 (0%)	
Ais	1 (0.51%)	1 (0.51%)		1(0.75%)	1(0.75%)	
I	13 (6.63%)	29 (14.80%)		13 (9.70%)	13 (9.70%)	
II	8 (4.08%)	8 (4.08%)		8 (5.97%)	8 (5.97%)	
III	55 (28.06%)	25 (12.76%)		20 (14.93%)	25 (18.66%)	
IV	34 (17.35%)	20 (10.20%)		24 (17.91%)	20 (14.93%)	
Therapy discontinuance	17 (8.67%)	38 (19.39%)	<.001	6 (4.48%)	33 (24.63%)	<.001
Cancer progression	71 (36.22%)	41 (20.92%)	.06	44 (32.84%)	38 (28.36%)	.38
Dead	3 (1.53%)	9 (4.60%)	.03	3 (2.24%)	9 (6.72%)	.13

AAH = atypical adenomatous hyperplasia, ADC = adenocarcinoma, Ais = adenocarcinoma in situ, NSCLC = non–small cell lung cancer, PSM = propensity score matching, SCC = squamous cell carcinoma.

Table 4

Comparison of different treatment methods and prognosis of the 196 NSCLC patients pre- and post-PSM.

	Pre-PSM			Post-PSM		
Items	**Control group (n = 112)**	**Experimental group (n = 84)**	***P* value**	**Control group (n = 67)**	**Experimental group (n = 67)**	***P* value**
Early stage	23 (11.73%)	39 (19.90%)		23 (17.16%)	22 (16.42%)	
Surgical treatment	17 (8.67%)	31 (15.82%)	.76	17 (12.69%)	20 (14.93%)	.24
Nonsurgical treatment	0 (0%)	1 (0.51%)	>.99	0 (0%)	0 (0%)	
Therapy discontinuance	6 (3.06%)	7 (3.57%)	.525	6 (4.48%)	2 (1.49%)	.24
Prognosis						
Stable	20 (10.20%)	34 (17.35%)	>.99	20 (14.93%)	20 (14.93%)	>.99
Progression	3 (1.53%)	4 (2.04%)	>.99	3 (2.24%)	1 (0.75%)	.61
Dead	0 (0%)	1 (0.51%)	>.99	0 (0%)	1 (0.75%)	.49
Late stage	89 (45.41%)	45 (22.96%)		44 (32.84%)	45 (33.58%)	
Surgical treatment	7 (3.57%)	4 (2.04%)	>.99	0(0%)	4 (2.99%)	.12
Nonsurgical treatment	71 (36.22%)	10 (5.10%)	<.001	34 (25.37%)	10 (7.46%)	<.001
Therapy discontinuance	11 (5.61%)	31 (15.82%)	<.001	0(0%)	31 (23.13)	<.001
Prognosis						
Stable	18 (9.18%)	0 (0%)	.001	0(0%)	0(0%)	
Progression	68 (34.70%)	37 (18.88%)	.51	41 (30.60%)	37 (27.61%)	.20
Dead	3 (1.53%)	8 (4.08%)	.01	3 (2.24%)	8 (5.97%)	.20

NSCLC = non–small cell lung cancer, PSM = propensity score matching.

Table 5

Reasons for discontinuation of therapy.

Items	Control group (n = 17)	Experimental group (n = 38)
Early stage	6 (10.91%)	7 (12.73%)
Patient refusal	5 (9.10%)	7 (12.73%)
Doctor suggestion	0 (0%)	0 (0%)
Physical weakness	1 (1.81%)	0 (0%)
COVID-19 infection	0 (0%)	0 (0%)
Late stage	11 (20.00%)	31 (56.36%)
Patient refusal	4 (7.27%)	5 (9.10%)
Doctor suggestion	0 (0%)	20 (36.36)
Toxicity	4 (7.27%)	4 (7.27%)
Physical weakness	3 (5.45%)	2 (3.64%)
COVID-19 infection	0 (0%)	0 (0%)

COVID-19 = coronavirus disease 2019.

2.5. Statistical analysis

SPSS version 22.0 (IBM Corp., Armonk, NY) software was used for statistical analyses. Continuous data were expressed as means ± standard deviation or as medians. The *t* test was used to compare normally distributed data with equal variances. The Mann–Whitney *U* test was used to compare nonnormally distributed data sets. Categorical data were expressed as counts and percentages. Comparisons between groups were performed using the chi-square test and Fisher exact probability test. Survival curves were analyzed using the Kaplan–Meier method. Indicators with statistically significant results were incorporated into a Cox regression analysis for multivariate analysis of risk factors for progress-free survival (PFS). Propensity score matching (PSM) was used for clinical characteristics to adjust for possible selection bias. A difference was considered to be statistically significant if the *P* value was <.05.

3. Results

3.1. Patient characteristics

Nine thousand ten patients hospitalized in Sichuan Science City Hospital between September 2019 and February 2020 participated in this study, including 4518 men and 4492 women. One hundred ninety-six NSCLC patients were confirmed by pathology and treated in our hospital, including 133 previously confirmed late-stage patients who received nonsurgical treatment and 63 newly confirmed patients. A flowchart diagraming the patient selection process is presented in Figure 1. The clinical characteristics of the 9010 patients are shown in Table 1. The clinical characteristics of the 63 newly confirmed patients are shown in Table 2.

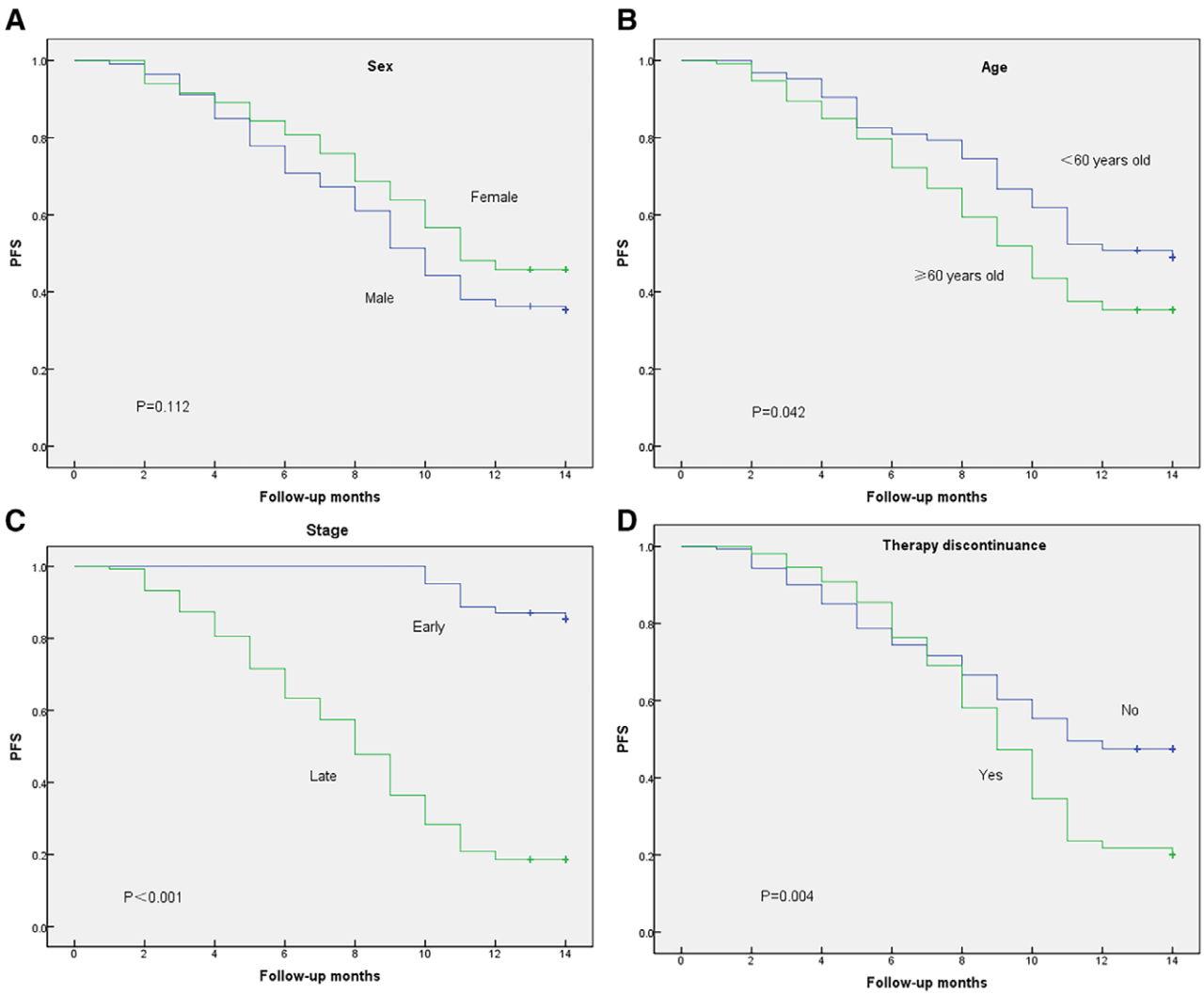

Figure 2. The PFS of sex (A), age (B), stage (C) and therapy discontinuance (D) pre-PSM. PFS = progress-free survival, PSM = propensity scores matching.

The 12 deaths that occurred during this study were cancer-specific, and the total mortality rate was 0.133% (12/9010). Among the 196 NSCLC patients, the difference in cancer progression between the 2 groups was not significant (P = .06), while the number of deaths in the control group was significantly lower than in the experimental group (P = .03) before PSM. After PSM, we determined that cancer progression and the number of deaths were not significantly different between the 2 groups. The clinical characteristics of the 196 NSCLC patients are shown in Table 3.

3.2. Treatment strategy evaluation

Sixty-two of the 196 NSCLC patients were early-stage cases, and the treatment methods and prognosis among them did not differ significantly before and after PSM. There were no significant differences in surgical treatment among the late-stage patients in surgical treatment. However, there were significant differences in nonsurgical treatments (P<.001) and discontinuation of therapy (P<.001) between the 2 groups before and after PSM. The prognosis of the late-stage patients was not significantly different after PSM. The comparison of different treatment methods

Table 6

Multivariate analysis of risk variables for cancer progression pre- and post-PSM.

	Pre-PSM HR (95% CI)	*P* value	Post-PSM HR (95% CI)	*P* value
Therapy discontinuance (yes vs no)	1.424 (0.987–2.074)	.07	1.007 (0.653–1.552)	.98
Age (≥60 yr old vs <60 yr old)	1.231 (0.820–1.850)	.32		
Stage (late vs early)	10.281 (5.170–20.447)	<.001	22.502 (8.949–56.584)	<.001

CI = confidence interval, HR = hazard ratio, PSM = propensity scores matching.

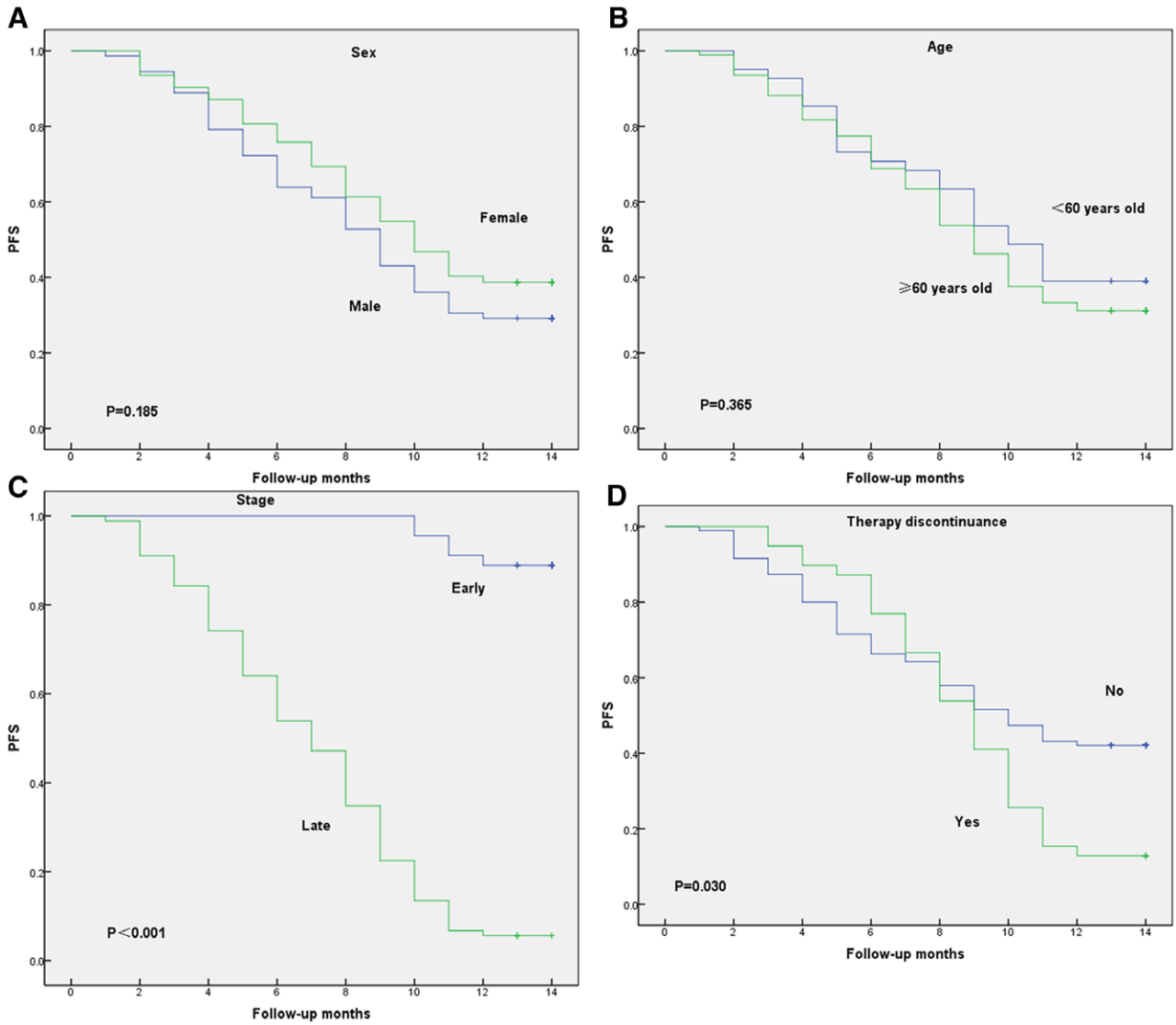

Figure 3. The PFS of sex (A), age (B), stage (C) and therapy discontinuance (D) post-PSM. PFS = progress-free survival, PSM = propensity scores matching.

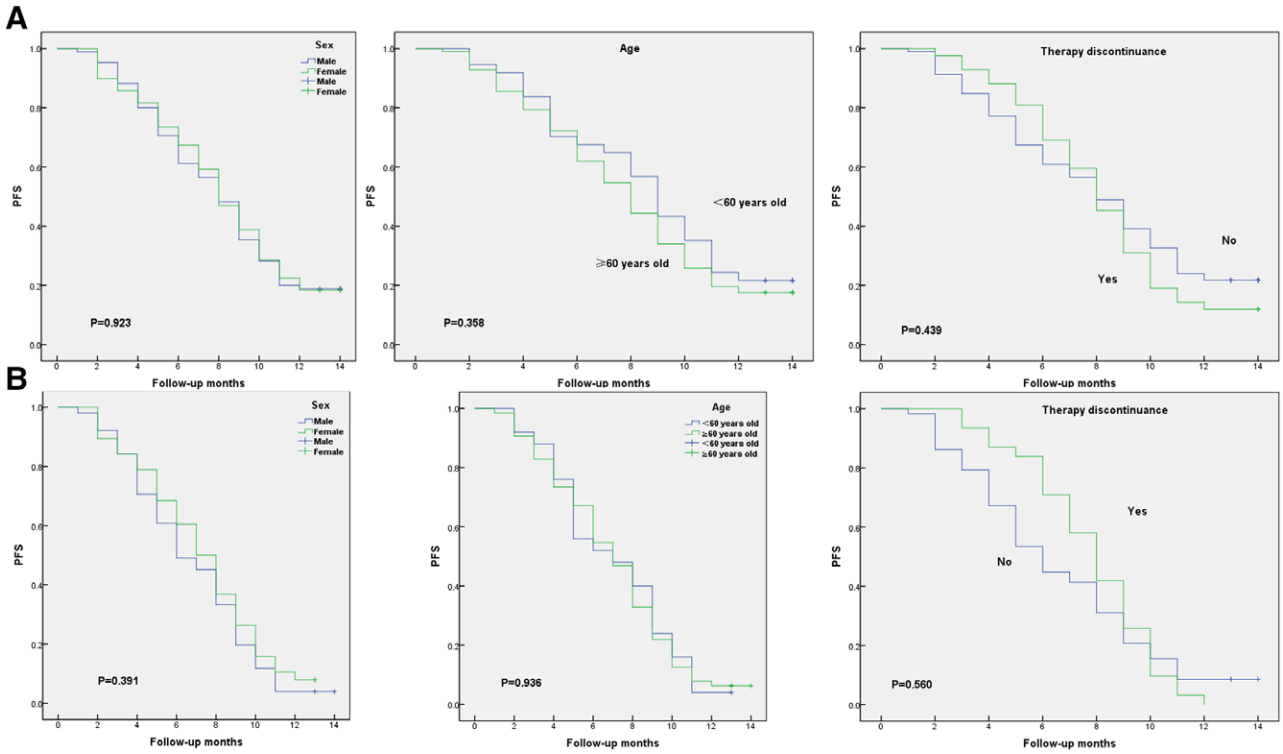

Figure 4. The PFS of late-stage patients before (A) and after (B) PSM. PFS = progress-free survival, PSM = propensity scores matching.

and prognosis of the 196 NSCLC patients are seen in Table 4. Of the 55 cases in which therapy was discontinued, only 18 late-stage patients returned to treatment after discontinuing therapy for 3 months. There were no cases that delayed therapy due to a COVID-19 infection or concern about infection. The reasons for the discontinuation of therapy are shown in Table 5.

3.3. Risk factor analysis for cancer progression

After PSM, the specific stage and discontinuation of therapy were the significant predictors of poor survival, based on 12-month PFS Kaplan–Meier curves (Fig. 3). Cox multivariate regression analysis showed that the stage was an independent predictor of PFS, but discontinuation of therapy was not (Table 6).

4. Discussion

At the beginning of the COVID-19 pandemic, we utilized progressive strategies for early-stage patients and conservative strategies for late-stage patients. When performing surgery, we developed a series of prevention programs in the surgical suites, including checking body temperature, wearing medical face masks and protective clothing, and utilizing laminar airflow in the surgery rooms.

As seen in Table 3, after PSM, the number of patients discontinuing therapy in the experimental group was significantly higher than in the control group ($P < .001$). This difference was highly apparent for the late-stage patients ($P < .001$; Table 4). However, Table 4 also shows that the differences in cancer progression and the number of deaths in late-stage patients between the 2 groups were not significant ($P = .20$) , and Figure 4 manifests that the PFS of undergoing therapy discontinuance or not in late-stage patients is not significantly different ($P = .56$). Therefore, discontinuing therapy for late-stage patients did not worsen their prognosis. This might have occurred because some late-stage patients returned to treatment within 3 months after therapy discontinuation, which did not significantly increase the possibility of cancer progression and death. This also could be why discontinuation of therapy was not an independent predictor of PFS, as noted in Figure 3 and Table 6. The European Society of Medical Oncology[12] described principles that classified 3 levels (high, medium, and low) of priorities for cancer care management. It is important to note that the European Society of Medical Oncology recommended a high priority for advanced NSCLC cases and that neoadjuvant treatment should be provided in potentially resectable stage IIIA cases during the COVID-19 pandemic. However, the National Institute for Health and Care Excellence suggests that anticancer treatments need to be prioritized at the highest level if curative treatment with a greater (>50%) chance of success is to be achieved; whereas adjuvant or neoadjuvant treatment should not be recommended as the highest priority if the treatment added only an intermediate (20%–50%) or a low (10%–20%) chance of cure in addition to surgery or other treatment provided at relapse.[13] Therefore, considering this study as well as the latter guideline, we believe it is optional to suspend treatment for <3 months for late-stage NSCLC patients because it does not significantly impact their prognosis. However, most patients should not delay treatment if there is a good chance that a successful curative treatment could be achieved.

Concerning early-stage NSCLC, most guidelines recommended surgical treatment when it was determined that there was a low risk for COVID-19 infection. For example, Cafarotti and Patella[14] established a risk stratification for lung cancer progression and COVID infection and suggested surgical treatment for NSCLC stages I to IIA when the infection risk was low. Shipe et al[15] proposed that immediate surgical biopsy of lung nodules suspicious for cancer in hospitals with low COVID-19 prevalence likely resulted in an improved 5-year survival rate. In this study, we did not verify whether discontinuing therapy would influence the prognosis of early-stage patients. We demonstrated that the prognosis among early-stage patients was not significantly different due to the progressive strategies used

with early-stage NSCLC patients. Therefore, we preferred not to carry out surgery aggressively for early-stage patients during the time of high risk of COVID-19, even though some studies reported that LSOLs might double in nodule size and progress from localized to regional or distant disease after a 3-month delay.[16,17]

We also observed in this study that the number of patients with unclear diagnoses and malignant LSOLs in the experimental group was significantly higher than in the control group ($P < .001$; Table 1), which was likely due to frequent CT imaging. It is known that chest CT imaging is critical in lung cancer screening. The National Lung Screening Trial Research of America found that 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false-positive results, and the rate of death from any cause was reduced in the low-dose CT group.[18] An Early Lung Cancer Action Project study showed that 85% of the CT-detected cancers were stage I, and the rate of cure for these malignancies was >80%.[19] Table 2 illustrates that most of the newly confirmed NSCLC cases were early-stage, which also is a beneficial result of widely performing CT imaging.

We observed a significantly higher number of late-stage patients, as shown in Tables 3 and 4. This might be due to an accumulation of previously confirmed late-stage patients who underwent ancillary therapies during the observation period, which resulted in several unavoidable extreme results seen in Table 3, Figure 2, and Figure 3.

Three types of limitations were associated with this study, including a limited number of cases, a relatively short observation period, and it was a retrospective study, which might reduce clinical relevance. However, the information gained from this study still offers additional guidance to clinicians. It is evident that we must deal with the current pandemic over the long term, and it has become normal that the pandemic has reoccurred sporadically in China. Therefore, based on our study, it is reasonable to temporarily suspend treatment for late-stage NSCLC patients in regions under quarantine restrictions for limited times.

5. Conclusions

For patients in geographical regions with a high risk for COVID-19 infections, temporarily suspending treatment for late-stage NSCLC patients is not likely to significantly impact their prognosis if they can return to treatment within 3 months of discontinuation.

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Reference

[1] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
[2] Chen H, Ai L, Lu H, et al. Clinical and imaging features of COVID-19. Radiol Infect Dis. 2020;7:743–50.
[3] Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 2020;7:4.
[4] Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21:335–7.
[5] Christine MC, Isabelle RC, Blay JY, et al. Lymphopenia in cancer patients and its effects on response to immunotherapy: an opportunity for combination with cytokines? J ImmunoTher Cancer. 2019;7:85.
[6] Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5:33.
[7] Rogado J, Pangua C, Serrano-Montero G, et al. Covid-19 and lung cancer: a greater fatality rate? Lung Cancer. 2020;146:19–22.
[8] Gosain R, Abdou Y, Singh A, et al. COVID-19 and cancer: a comprehensive review. Curr Oncol Rep. 2020;22:53.
[9] Kumar S, Chmura S, Robinson C, et al. Alternative multidisciplinary management options for locally advanced NSCLC during the coronavirus disease 2019 global pandemic. J Thorac Oncol. 2020;15:1137–1146.
[10] Mazzone PJ, Gould MK, Arenberg DA, et al. Management of lung nodules and lung cancer screening during the COVID-19 pandemic: CHEST expert panel report. J Am Coll Radiol. 2020;17:845–854.
[11] Raskin J, Lebeer M, De Bondt C, et al. Cancer in the time of COVID-19: expert opinion on how to adapt current practice. Eur Respir J. 2020;55:2000959.
[12] Passaro A, Addeo A, Von Garnier C, et al. ESMO management and treatment adapted recommendations in the COVID-19 era: lung cancer. ESMO Open. 2020;5:e000820.
[13] NICE. COVID-19 rapid guideline: delivery of systemic anticancer treatments. In: National Institute for Health and Care Excellence: Clinical Guidelines. London: National Institute for Health and Care Excellence; 2021.
[14] Cafarotti S, Patella M. Lung cancer surgical management during the outbreak of coronavirus disease 2019. J Thorac Oncol. 2020;15:e81.
[15] Shipe ME, Haddad DN, Deppen SA, et al. Modeling the impact of delaying the diagnosis of non-small cell lung cancer during COVID-19. Ann Thorac Surg. 2021;112:248–54.
[16] Gould MK, Sanders GD, Barnett PG, et al. Cost-effectiveness of alternative management strategies for patients with solitary pulmonary nodules. Ann Intern Med. 2003;138:724–35.
[17] Edelsberg J, Weycker D, Atwood M, et al. Cost-effectiveness of an autoantibody test (EarlyCDT-Lung) as an aid to early diagnosis of lung cancer in patients with incidentally detected pulmonary nodules. PLoS One. 2018;13:e0197826.
[18] Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395–409.
[19] Henschke CI, McCauley DI, Yankelevitz DF, et al. Early lung cancer action project: a summary of the findings on baseline screening. Oncologist. 2001;6:147–52.