Original Article

Incidence and risk factors of pneumonia in diffuse large B-cell lymphoma patients receiving first line R-CHOP/R-CHOP-like immunochemotherapy: a retrospective study of 287 patients in single center

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Background: Diffuse large B-cell lymphoma (DLBCL) patients may develop pneumonia during immunochemotherapy. The purpose of this retrospective study was to determine the incidence of and risk factors for pneumonia.

Methods: By retrospectively searching the hospital's computer-database, we reviewed the records of DLBCL patients who underwent the first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)/R-CHOP-like immunochemotherapy at our institution from January 2012 to June 2019. Statistical analyses were conducted to calculate the odds ratio (OR) of characteristics and identify the risk factors of pneumonia for these patients.

Results: In total, 287 DLBCL patients were recruited to this study. Among them, 84 (29.3%) patients developed pneumonia during treatment. The incidence of severe pneumonia was 19.4% (18/93) with a 33.3% mortality rate (6/18). Pneumonia was associated with inferior progression-free survival (PFS) [hazard ratio (HR) 1.78, 95% confidence interval (CI): 1.05 to 3.00, P=0.016]. Through multivariate logistic regression analysis, age (OR =1.030, 95% CI: 1.005 to 1.055), advanced stage (OR =2.176, 95% CI: 1.015 to 4.669), comorbidity of chronic kidney disease (CKD) (OR =11.794, 95% CI: 2.444 to 56.910), severe agranulocytosis (OR =8.777, 95% CI: 4.457 to 17.285), and pneumonia at onset (OR =9.548, 95% CI: 3.734 to 24.413) were identified as risk factors for pneumonia during the course of immunochemotherapy.

Conclusions: Pneumonia has a negative impact on survival in DLBCL patients receiving the first-line R-CHOP/R-CHOP-like regimen. For patients with risk factors, surveillance should be emphasized to prevent pneumonia.

Keywords: Diffuse large B-cell lymphoma (DLBCL); pneumonia; immunotherapy; risk factor

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Introduction

The incidence of non-Hodgkin's lymphoma (NHL) has risen steadily in the past decades. In China, NHL ranked the 8th cause of cancer incidences and the 11th cause of cancer-related death in 2015 (1). Diffuse large B-cell lymphomas (DLBCL) is the most common NHL subtype (2). During the past 2 decades, the frontline rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone

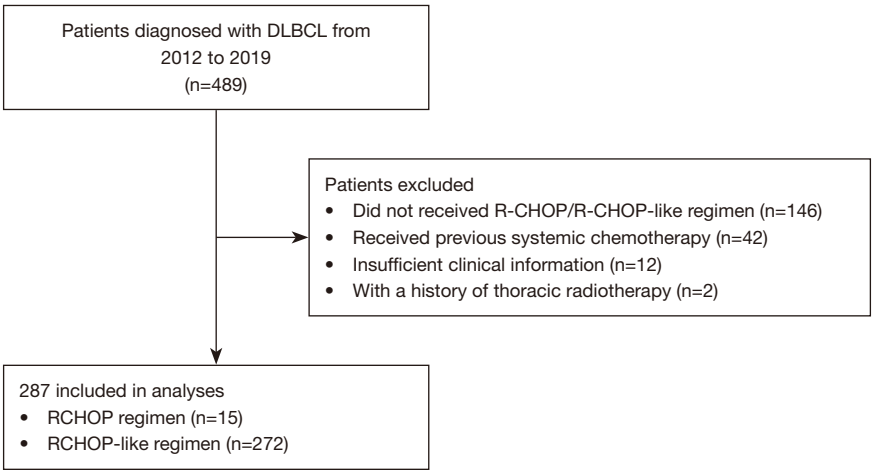


Figure 1 Methodology outline. DLBCL, diffuse large B-cell lymphoma.

(R-CHOP) regimen has dramatically improved the survival of DLBCL patients. It is recognized as the most effective regimen for DLBCL. Nevertheless, the challenges of drug toxicities are still severe. Common adverse events of immunochemotherapy are hematological toxicity, neurologic toxicity, nausea or vomiting, infection, etc. (3). It was estimated that infectious etiologies (75%) accounted for the majority of respiratory complications in CD20 positive NHL patients after rituximab-containing chemotherapy (4). Data from a real-world study of the first-line R-chemo in Chinese patients with DLBCL showed the incidence of infectious pneumonia was 11.1% (5). Acute pulmonary infection can be serious or even fatal. In general, it often leads to delayed treatment and greater medical expenses. However, risk factors for infectious pulmonary complications in DLBCL patients during rituximab-containing chemotherapy are still unclear. The aim of this retrospective study was to analyze the incidence, clinical characteristics, treatment outcomes and risk factors of pneumonia in DLBCL patients during the first-line R-CHOP/R-CHOP-like immunochemotherapy. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3280).

Methods

A case-control study was used to explore the risk factors of pneumonia. The electronic database of Huadong Hospital Affiliated to Fudan University was retrospectively reviewed to identify all patients diagnosed with DLBCL from January 2012 to June 2019. We observed and recorded the occurrence of pneumonia from the beginning of immunochemotherapy to 30 days after the last cycle of treatment. All survival analyses were restricted to 2 years of follow-up after diagnosis. Progression-free survival (PFS) was defined as the time from diagnosis to the date of disease progression or death due to any cause. Overall survival (OS) was defined as the time from diagnosis to the death from any cause or last date of follow-up. The inclusion criteria for the study were as follows: (I) histologically confirmed as CD20+ DLBCL; (II) underwent the first-line R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-CHOP-like (epirubicin, pirarubicin or pegylated liposomal doxorubicin was used instead of doxorubicin) regimen at our institute. Patients were excluded if they had history of thoracic radiotherapy or lack of sufficient clinical information in their chart.

A total of 287 patients with DLBCL were finally enrolled (*Figure 1*). The R-CHOP/R-CHOP-like regimens were generally given to patients every 3 weeks. The dosage was adjusted to 80% for patients 70–79 years of age and 50% for patients over 80. Besides routine imaging examination, patients who had symptoms of acute respiratory infection underwent additional chest computed tomography (CT) scan or chest radiography. The following clinical data were collected: age, gender, Ann Arbor stage, smoking history, immunochemotherapy regimens, laboratory results (baseline hemoglobin level, baseline serum albumin level, routine blood test during follow-up), and comorbidities of diabetes, chronic kidney disease (CKD; estimated glomerular filtration rate <60 mL/min/1.73 m^2 for ≥3 months),

cardiovascular, and pulmonary disease. Agranulocytosis induced by immunochemotherapy was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf). Hemoglobin levels were analyzed by colorimetry on Sysmex XN Hematology Analyzer (Sysmex Corp., Hyogo, Japan), with the following reference range: male 130–175 g/L, female 115–150 g/L. Serum albumin concentrations were assessed by bromocresol green methods on Roche Cobas 8000 (Roche, Basel, Switzerland), reference range: 35–52 g/L.

Pneumonia is defined as an acute infection of the pulmonary parenchyma caused by a pathogenic microorganism. Referring to American Thoracic Society consensus guidelines (6), pulmonary inflammatory lesions must be identified by chest CT scan or chest radiography in conjunction with respiratory symptoms and clinical exam as follows: (I) a new or worsened cough and sputum; (II) fever; (III) lung consolidation signs and/or wet rales; (IV) white blood cell >10,000 cells/mm^3, or <4,000 cells/mm^3, with or without nuclear shift to left. Patients who met the following criteria were diagnosed with severe pneumonia: 1 of 2 major criteria: (I) invasive mechanical ventilation; (II) septic shock with the need for vasopressors; or 3 of 9 minor criteria: (I) respiratory rate >30/min; (II) arterial oxygen partial pressure/fractional inspired oxygen (PaO_2/FiO_2) ratio ≤250; (III) multilobar infiltrates; (IV) confusion/disorientation; (V) uremia (blood urea nitrogen (BUN) level ≥20 mg/dL); (VI) leukopenia (white blood cell (WBC) count <4,000 cells/mm^3); (VII) thrombocytopenia (platelet count <100,000 cells/mm^3); (VIII) hypothermia (core temperature <36 ℃); (IX) hypotension requiring aggressive fluid resuscitation.

This study was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University (No. 2020K009). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

Statistical analysis

A descriptive analysis was performed. Continuous data were assessed for normality by Kolmogorov-Smirnov test. Non-normally distributed variables were presented as the median and interquartile range. Mann-Whitney U-test was used for group comparisons of non- normally distributed data. Univariate comparisons for categorical data between groups were assessed using chi-square or Fisher exact test if necessary. Logistic regression was performed including all factors with P value <0.2 in the bivariate analysis, using a backward stepwise approach, to determine the predictive factors regarding pneumonia. The log-rank test was used to analyze PFS and OS. The results were expressed as Kaplan-Meier plots using MedCalc version 18.2.1 (MedCalc Software, Ostend, Belgium). A P value <0.05 was regarded as statistically significant in 2-sided tests. All statistical analyses were performed using the SPSS statistical software version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Participant characteristics

Between January 2012 and June 2019, 489 consecutive DLBCL patients were admitted to Huadong Hospital. In total, 287 patients were enrolled in this study according to inclusion and exclusion criteria (*Figure 1*). The median age was 64 years (range, 24–90 years). A total of 26 (9.1%) patients (feeble or aged ≥80 years) received an R-mini-CHOP/like regimen. Moreover, 63 (22.0%) patients' dosages were reduced by 20% on account of drug toxicities or combined mild organ dysfunction. We established 2 cohorts: the pneumonia cohort and the non-pneumonia cohort. The clinical features of patients were summarized in *Table 1*. In total, 143 (49.8%) patients had complications which manifested clinical symptoms or needed medication. We observed that 37 (12.9%) patients experienced pneumonia at onset before initial treatment of lymphoma, all of whom received adequate and effective antibiotics treatment before the first course of immunochemotherapy.

In the pneumonia cohort, more patients had current smoking history (28.6% *vs.* 16.7%, P=0.000), advanced stage (84.5% *vs.* 68.0%, P=0.004), B systems (56.0% *vs.* 39.4%, P=0.01), and pneumonia at onset before treatment (28.6% *vs.* 6.4%, P=0.000). Except for CKD (11.9% *vs.* 1.5%, P=0.000), numbers of patients with other comorbidities were similar between the 2 cohorts. Compared with the non-pneumonia cohort, baseline serum albumin level was lower in the pneumonia cohort (39 *vs.* 40 g/L, P=0.035), but the hemoglobin level had no significant difference. Severe agranulocytosis after treatment was more common in the pneumonia cohort (65.5% *vs.* 23.6%, P=0.000).

Clinical features of patients with pneumonia

In total, 93 pneumonia episodes were observed among

Table 1 Comparison of patient characteristics between the pneumonia and non-pneumonia cohorts

Characteristics	Pneumonia		P value
	Yes, n=84	No, n=203	
Age (years)	67 (57–75)	64 (54–71)	0.014[c]
Gender, n (%)			0.018[d]
Male	55 (65.5)	102 (50.2)	
Female	29 (34.5)	101 (49.8)	
Current smoking[a], n (%)	24 (28.6)	34 (16.7)	0.000[d]
Advanced stage: Ann Arbor III/IV, n (%)	71 (84.5)	138 (68.0)	0.004[d]
B systems[b], n (%)	47 (56.0)	80 (39.4)	0.010[d]
Bone marrow involvement, n (%)	11 (13.1)	22 (10.8)	0.585[d]
Lung involvement, n (%)	8 (9.5)	8 (3.9)	0.061[d]
Comorbidity, n (%)			
Diabetes	10 (11.9)	35 (17.2)	0.258[d]
CKD	10 (11.9)	3 (1.5)	0.000[d]
Cardiovascular disease	31 (36.9)	57 (28.1)	0.140[d]
Pulmonary disease	15 (17.9)	30 (14.8)	0.514[d]
Baseline laboratory data (g/L)			
Serum albumin	39.0 (32.0–43.0)	40.0 (36.0–44.0)	0.035[c]
Hemoglobin	116.0 (98.8–137.8)	123.0 (108.5–134.8)	0.495[c]
Severe agranulocytosis (III/IV) after treatment, n (%)	55 (65.5)	48 (23.6)	0.000[d]
Pneumonia at onset, n (%)	24 (28.6)	13 (6.4)	0.000[d]

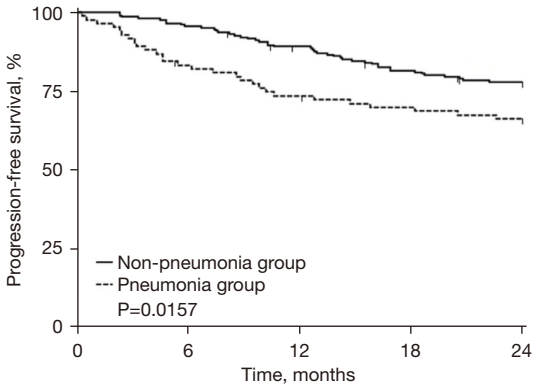
Data are median (IQR) and n (%). [a], current smoking was defined as having smoked ≥100 cigarettes during their lifetime and still smoked or had quit smoking within the preceding year; [b], B systems was defined as disease-related fevers (>38 ℃), night sweats, or weight loss (≥10% of body weight in 6 months); [c], P values were calculated using Mann-Whitney U-test (two-tailed); [d], P values were calculated using Chi-square or Fisher exact test (two-tailed). CKD, chronic kidney disease.

all patients. A total of 84 (29.3%) patients developed pneumonia, out of whom 8 (9.5%) experienced pneumonia recurrence during immunochemotherapy. The treatment was delayed in 64 (68.8%) cases of pneumonia with a median interruption time of 13 days (range, 1–54 days). Premature termination of immunochemotherapy was occurred in 9 (9.7%) cases. The median number of immunochemotherapy cycles before pneumonia was 3 (IQR, 2–4). Severe pneumonia was experienced by 19.4% (18/93), among whom 6 (33.3%) died from serious infection and respiratory failure.

To identify the pathogens, sputum and/or blood culture were conducted. For the cases with positive sputum cultures, the bacteria involved were *Klebsiella* (n=1), *Enterococcus faecalis* (n=2), *Streptococcus pneumonia* (n=3), *Acinetobacter baumannii* (n=1), *Haemophilus parainfluenzae* (n=2), and *Stenotrophomonas maltophilia* (n=1). A total of 14 cases were confirmed as fungal infection and 2 cases were diagnosed as *Pneumocystis jiroveci* infection. There were 6 patients diagnosed with a co-infection of bacteria and fungi. The pathogen remained unknown in the other 70 cases.

Risk factors for infectious pulmonary complication

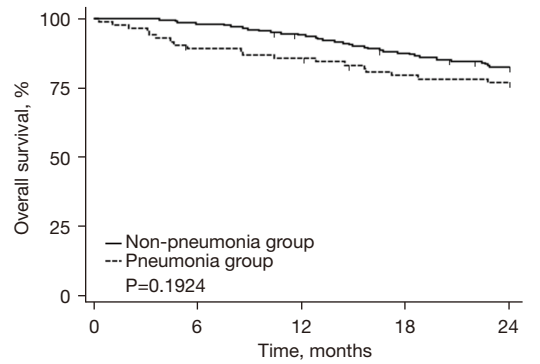
Compared to the non-pneumonia group, a significantly worse PFS was observed in the pneumonia group (HR 1.78, 95% CI: 1.05–3.00, P=0.016) (*Figure 2*), with a 2-year PFS rate of 66.3% (95% CI: 56.1–76.5%) and 78.1% (95% CI: 72.4–83.8%), respectively (P=0.039). No significant differences were observed in OS (HR 1.45, 95%



Number at risk

Non-pneumonia	203	194	178	162	152
Pneumonia	84	68	60	57	54

Figure 2 Kaplan-Meier estimates of PFS between two cohorts. PFS, progression-free survival.



Number at risk

Non-pneumonia	203	199	189	175	163
Pneumonia	84	73	70	63	62

Figure 3 Kaplan-Meier estimates of OS between two cohorts. OS, overall survival.

CI: 0.79–2.63, P=0.192) (*Figure 3*), with 2-year OS rate of 77.0% (95% CI: 68.0–86.0%) in the pneumonia group and 82.6% (95% CI: 77.3–87.9%) in the non-pneumonia group (P=0.289). Thus, we inferred that pneumonia had a negative impact on survival due to death and treatment delay.

To investigate the risk factors of pneumonia in these DLBCL patients, clinical parameters were analyzed in a binary logistic regression model (*Table 2*). The multivariate logistic regression model identified 5 independent predictors of pneumonia: age (OR =1.030, 95% CI: 1.005–1.055, P=0.019), advanced stage (OR =2.176, 95% CI: 1.015–4.669, P=0.046), complicated with CKD (OR =11.794, 95% CI: 2.444–56.910, P=0.002), severe agranulocytosis (OR =8.777, 95% CI: 4.457–17.285, P=0.000) and pneumonia at onset (OR =9.548, 95% CI: 3.734–24.413, P=0.000).

Discussion

The international prognostic index (IPI), results of positron emission tomography-computed tomography (PET-CT) scan and biological subtypes have been considered to provide accurate prognostic information. The applications of rituximab apparently increase the response rates and prolong the survival time. It was confirmed that the addition of rituximab didn't increase the occurrence of adverse events. Common adverse events of immunochemotherapy were leukocytopenia, infection, neurotoxicity, etc. (7). However, it is noteworthy that respiratory complications contributing to shortened survival time and lower quality of life are common in lymphoma patients receiving immunochemotherapy. Infectious etiologies including pneumonia account for 75% of the respiratory complications (4). Patients developing pneumonia during immunochemotherapy are likely experience prolonged hospitalization and increased mortality risk. We conducted this retrospective study to identify the risk factors of pneumonia during immunochemotherapy and its impact on survival.

In this study, pneumonia was reported in 29.3% of DLBCL patients during immunochemotherapy. Due to discontinuation or delay in treatment and death caused by pneumonia, those patients' PFS was significantly inferior to patients without pneumonia. There was no significant difference in OS. We speculated that post-line therapy had a positive impact on survival. The morbidity of pneumonia in our study was higher than data in previous studies. Lugtenburg *et al.* reported that the incidence rate of pneumonia was 5.6% (31/557) in DLBCL patients receiving R-CHOP regimens as first-line therapy (8). Moreover, a retrospective analysis by Lim *et al.* reported the incidence rate of pulmonary infection in NHL patients treated with CHOP or R-CHOP as the first induction therapy was 12% (12/100) (9). Reasons for the discordant results might be due to the different study populations. First, advanced stage (Ann Arbor stage III/IV) accounted for 72.8% in our study. This was higher than the 68.0% in Lugtenburg's study (8) as well as 46.0% in Lim *et al.*'s report (9). In our analysis, advanced stage was significantly associated with pneumonia. Higher tumor burden usually means greater impact on organ function and worse performance status. Consistent with our findings, Meng *et al.* demonstrated that disease stage (III–

Table 2 Binary logistic regression analysis of risk factors for pneumonia

Factors	Univariate logistic analysis			Multivariate logistic analysis		
	OR	95% CI	P value	OR	95% CI	P value
Gender	1.415	0.849 to 2.357	0.183			
Age	1.022	1.003 to 1.042	0.024	1.030	1.005 to 1.055	0.019
Smoking	2.600	1.480 to 4.568	0.001			
Advanced stage	3.102	1.600 to 6.014	0.001	2.176	1.015 to 4.669	0.046
B systems	2.008	1.204 to 3.349	0.008			
Lung involvement	2.300	0.834 to 6.344	0.108			
Chronic kidney disease	12.179	2.609 to 56.836	0.001	11.794	2.444 to 56.910	0.002
Cardiovascular disease	1.923	0.797 to 4.638	0.145			
Severe agranulocytosis	5.503	3.185 to 9.511	0.000	8.777	4.457 to 17.285	0.000
Pneumonia at onset	5.625	2.659 to 11.901	0.000	9.548	3.734 to 24.413	0.000
Serum albumin	1.929	1.107 to 3.363	0.020			

OR, odds ratio; CI, confidence interval.

IV) was an independent factor of interstitial pneumonitis in patients with DLBCL receiving immunochemotherapy (10). Secondly, aging was another reason for high incidence of pneumonia. Physiological and immunological changes with age contributed to the increased frequency and severity of respiratory tract infections (11,12). It was nevertheless noteworthy that although we reduced the dosage according to age, elderly patients were more susceptible to pneumonia. Pneumonia was reported by Wu *et al.* in 11.1% of DLBCL patients receiving first line R-Chemo. However, the median age of this study population was 57.2 years, which was younger than the 64 years old in our study (5). Certainly, differences in treatment schemes and diseases were also important reasons affecting the results.

Pneumonia risk was also associated with CKD. Both innate and adaptive immunity of CKD patients are impaired. Increased apoptosis, reduced differentiation, and dysfunction of immune cells have been shown to be associated with the vulnerability of infection (13). Research on a large-scale population confirmed the risk of pneumonia was 1.97-fold higher in patients with CKD than patients without CKD. The result showed CKD might be an independent risk factor for pneumonia (14). Pneumonia is one of common causes of hospital admission in patients with CKD. Compared with the general population, the incidence rate difference for pneumonia was 4.4/1,000 person-years (15), which is consistent with our findings. Despite the reduction in dosage to avoid adverse reactions, the risk of pneumonia was 11.8-fold higher in patients with CKD compared with non-CKD patients. These data suggest that CKD is independently associated with increased risk of pneumonia.

Infection is one of the common initial symptoms in patients of lymphoma. As a reflection of a frail condition, a past history of pneumonia has been identified as an independent risk factor for pneumonia recurrence in the general population (16). In our study, although adequate and effective antibiotics treatment were given, the rate of recurrent pneumonia in patients with pneumonia at onset was still up to 64.9% (24/37). It has been confirmed that immune deficiency is one of the main reasons for pneumonia recurrence (17). Seeing that immune deficiency was involved in tumorigenesis and development of DLBCL (18,19), patients with pneumonia at onset were more likely to experience pneumonia after immunochemotherapy. Our study showed that the risk of pneumonia was 9.54-fold higher in this special population.

Our study had several limitations. Firstly, due to its retrospective design, patients' medical history data and laboratory results might have been incomplete. Some patients did not undergo microbiological culture, which led to failure to identify the pathogenic classifications of their pneumonias. Secondly, owing to the lack of pathogenic evidence, we ruled out all the patients with interstitial pneumonia diagnosed by CT alone. Although drug-related

interstitial pneumonia was excluded, some cases of infection were omitted inevitably. Thirdly, the observation period of our study was short, so we were unable to identify the long-term effects of immunochemotherapy on systemic organs including respiratory system. Additionally, most patients received the R-CHOP-like regimen. Application of different anthracyclines might be a confounding factor that affected the results.

Conclusions

In summary, our study indicated several independent risk factors associated with pneumonia during immunochemotherapy in DLBLC patients. Patients of old age, advanced stage, CKD, severe agranulocytosis, or pneumonia at onset were more likely to experience pneumonia. Taking into account that pneumonia leaded to shorter PFS, it is suggested that prevention and surveillance should be emphasized for these patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-3280

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-3280

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-3280). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University (No. 2020K009). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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