Original Article

Predictors and reasons for unplanned early rehospitalization in lung transplant recipients: a retrospective cohort study

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Background: Unplanned early rehospitalization (UER) is common among lung transplant recipients, but its incidence varies among lung transplant centers. This study aimed to analyze the incidence, causes and predictors of UER in a lung transplant center in China and to explore the impact of preoperative nutritional risk status, postoperative duration of mechanical ventilation (MV) and extracorporeal membrane oxygenation support in the intensive care unit on unplanned readmission in lung transplant patients.

Methods: This study was conducted in one of the largest lung transplant centers in China. We collected demographic and clinical data from lung transplant recipients who underwent transplantation and were discharged in 2022. Predictors of UER within 30 days after discharge were analyzed through a retrospective cohort study.

Results: A total of 99 patients were included in this study. The incidence of UER was 29.3%. The three most common reasons were chest distress with shortness of breath (38%), cough with expectoration (21%), and fever (21%). Multivariate analysis revealed that the postoperative MV duration [odds ratio (OR) =1.027; 95% confidence interval (CI): 1.008–1.046; P=0.004] and preoperative Nutrition Risk Screening 2002 (NRS-2002) score (OR =1.615; 95% CI: 1.189–2.194; P=0.002) were significant risk factors for UER.

Conclusions: Patients with higher preoperative NRS-2002 scores and longer postoperative MV duration had a greater risk of UER within 30 days after initial discharge. More research is needed to determine whether improving preoperative nutritional risk status and shortening the duration of MV can reduce UER in patients.

Keywords: Lung transplantation; rehospitalization; unplanned early rehospitalization (UER)

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Introduction

Lung transplantation (LT) is an effective means of treating end-stage lung disease and can effectively prolong the life of patients. According to data reported by the International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation, approximately 4,500 lung transplants are performed worldwide each year, and the number of lung transplants continues to increase (1). LT is the most difficult type of organ transplantation; many postoperative complications can occur, and the rates of these complications increase significantly over time, which is the main reason why the incidence of rehospitalization after LT remains high compared with that of other medical surgical populations (2).

For lung transplant recipients, it is difficult to avoid unplanned rehospitalization (UR) after discharge. The occurrence of UR may indicate obstruction of the rehabilitation process and has a negative effect on quality of life and resource utilization (3). It has been shown that unplanned early rehospitalization (UER) soon after initial discharge after LT is associated with an increased risk of mortality, and the cumulative burden of multiple readmission is associated with worse long-term survival (4,5). Therefore, it is particularly important to identify the predictors of UER for lung transplant recipients and to develop targeted interventions to avoid UER. This information may help improve the survival duration for lung transplant recipients.

According to the available studies, the incidence of UER in lung transplant patients within 30 days after initial discharge ranged from 29.8% to 45.4% (3-8). Previous research has identified some preventable or modifiable risk factors. In Osho *et al.*'s study, the occurrence of any post-transplant complication was a risk factor for 30-day unplanned hospital readmission (7). Mollberg *et al.* reported that patients who were discharged for inpatient rehabilitation were less likely to be readmitted within the first 30 days after discharge (5). According to Courtwright *et al.*'s study, frailty at discharge, defined as a Short Physical Performance Battery (SPPB) score <6, increased the risk of UER (6). However, these findings are still insufficient to fully explain the factors influencing UER. Many potential factors still need to be further explored.

Sufficient nutrition is the basis for the successful recovery of lung transplant recipients. Malnutrition in LT candidates increases the risk of postoperative complications (9). Therefore, we believe that determining whether preoperative nutritional risk status can predict UER is worth exploring. Intensive care fosters an enhanced role in the entire process of LT. Mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO) are two important life support tools used during intensive care. Early tracheal extubation can shorten hospital length of stay and promote pulmonary rehabilitation, which may decrease the risk of UER (10). Controversy remains regarding the optimal timing for ECMO removal. Minqiang *et al.* (11) reported that delayed weaning from ECMO increased the risk of infection, primary graft dysfunction, and renal dysfunction, which may promote the occurrence of UER. However, Li *et al.* (12) reported that patients who underwent delayed weaning from ECMO had fewer complications and shorter hospital stays. Thus, further studies are needed to understand exactly how MV and ECMO affect lung transplant recipients and to explore new strategies to reduce the incidence of UER.

In China, there have not been any relevant studies published on this topic. Given the differences in medical management strategies, health care systems, and ethnicities, UER of lung transplant patients may have different causes and predictors in China. As one of the largest lung transplant centers in China, we conducted a retrospective cohort study of patients who underwent LT during 2022. We analyzed the current incidence, main causes and predictors of UER. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1302/rc).

Highlight box

Key findings

- Lung transplant recipients with higher preoperative Nutrition Risk Screening 2002 scores and longer postoperative mechanical ventilation (MV) duration had a greater risk of unplanned early rehospitalization within 30 days after initial discharge.

What is known and what is new?

- The incidence of unplanned early rehospitalization after lung transplantation remains high. The occurrence of any post-transplant complication and frailty at discharge increases the risk of unplanned early rehospitalization. However, there are still many potential factors that need to be further explored.
- We aim to explore the impact of preoperative nutritional risk status, postoperative duration of mechanical ventilation and extracorporeal membrane oxygenation support in the intensive care unit on unplanned readmission in lung transplant patients.

What is the implication, and what should change now?

- Improving preoperative nutritional risk status and shortening the duration of MV may help to reduce unplanned early rehospitalization in lung transplant patients. More research is needed to determine the conclusion.

Methods

Study design

This was a retrospective cohort study conducted at the Second Affiliated Hospital of Zhejiang University School of Medicine. We selected patients who underwent LT and survived to discharge in 2022. Patients younger than 18 years and patients who underwent multiorgan combination transplantation or secondary LT were excluded. The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013). This study was approved by the Ethical Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (No. 2023-0862). Written informed consent was waived by the ethics committee due to the anonymized retrospective nature of the analysis.

Data collection

In this study, UER was defined as readmission within 30 days after initial discharge due to various unexpected causes. Scheduled rehospitalizations, such as a follow-up for tracheoscopy, were excluded. Medical information within 30 days after discharge was retrospectively extracted from the electronic medical record system (EMRS). Two researchers analyzed the admission summary data, determined the reason for rehospitalization, and identified patients with UER. Based on clinical experience and literature analysis, we identified demographic and clinical variables that could lead to UER, and all variables were extracted from the EMRS. The variables included demographic characteristics (gender, age, education and marital status), preoperative condition [diagnosis, body mass index, comorbidities, hemoglobin, albumin, Activity of Daily Living (ADL), Nutrition Risk Screening 2002 (NRS-2002) score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score], surgery-related characteristics (type of lung transplantation, operation duration, whether it is a rescue lung transplantation), postoperative status [ECMO support duration, mechanical ventilation duration, length of intensive care unit (ICU) stay and length of hospital stay].

The APACHE II score is the sum of an acute physiology score (including 12 physiological variables, such as temperature, mean arterial pressure, heart rate), an age score and a chronic health evaluation score. The range of the total APACHE II score is from 0 to 71 points. The higher the score, the severer the illness. The length of ICU stay was calculated from the date of transplantation to the date of transfer out of the ICU. The length of hospital stay was calculated from the date of transplantation to the date of discharge.

Statistical analysis

For the demographic and clinical characteristics, categorical variables were expressed as the frequency and composition ratio, and continuous variables were expressed as the mean ± standard deviation (normal distribution) or median and interquartile range (nonnormal distribution). Levene's tests were conducted to evaluate variance equality. For the comparison of demographic and clinical characteristics between patients with and without UER, we used Student's *t*-tests for normally distributed continuous variables, Mann-Whitney *U* tests for nonnormally distributed continuous variables, and Chi-squared tests or Fisher's exact tests for categorical variables. Variables with P<0.15 in the univariate analysis were included in a multivariate logistic regression analysis. Parameter selection for final regression models was performed by forward elimination. We performed all analyses using the software package SPSS (Version 22, IBM Corp., Armonk, NY, USA).

Results

Study cohort

A total of 99 lung transplant recipients were eligible for study participation. The demographic and clinical characteristics of the cohort are listed in *Table 1*.

Reasons for UER in lung transplant recipients

The three most common causes of UER in lung transplant patients according to the presenting symptoms were chest distress with shortness of breath (38%), cough with expectoration (21%), and fever (21%), followed by anorexia (7%), palpitation (3%), hyperpotassemia (3%), excessive tacrolimus concentration (3%), and hypercapnia (3%). *Table 2* provides the reasons for UER.

Characteristics of lung transplant patients with UER

Among the 99 lung transplant recipients in the cohort, 29 (29.3%) experienced UER within 30 days after initial discharge. A comparison of the demographic and clinical characteristics of the lung transplant recipients stratified by UER is shown in *Table 3*. According to the univariate analysis, the NRS-2002 score, APACHE II score, duration of postoperative ECMO support, duration of postoperative MV, length of ICU stay and length of hospital stay after LT were significantly associated with UER (P<0.05).

All variables with a P value <0.15 in the univariate analysis were considered for inclusion in the final multivariate model. The variables that met our inclusion criteria were age (P=0.054), education (P=0.07),

Table 1 Demographic and clinical characteristics of the study cohort (n=99)

Characteristics	Values
Demographic characteristics	
Age (years)	56.31±10.49
Male	88 (88.9)
Education	
Elementary school and below	27 (27.3)
Junior high school	25 (25.3)
Senior high school	16 (16.2)
College degree or above	31 (31.3)
Marital status	
Married	95 (96.0)
Single	3 (3.0)
Divorced or widowed	1 (1.0)
Preoperative condition	
Diagnosis	
Restrictive disease	63 (63.6)
Obstructive disease	25 (25.3)
Other	11 (11.1)
Body mass index (kg/m^2)	20.58±4.16
Pre-existing comorbidities	
Diabetes mellitus	10 (10.1)
Hypertension	10 (10.1)
Coronary atherothrombotic disease	25 (25.3)
Epstein-Barr virus infection	14 (14.1)
Albumin (g/L)	35.97±4.33
Hemoglobin (g/L)	134.49±19.76
ADL	
≥60	85 (85.9)
40–59	6 (6.1)
<40	8 (8.1)
NRS-2002	2 (1–4)
APACHE II	7.81±2.93
Surgery-related characteristics	
Urgent lung transplantation	4 (4.0)
Bilateral transplant	47 (47.5)
Duration of surgery (hours)	4.87±1.20
Postoperative condition	
Duration of ECMO support (hours)	15.67 (10.50–18.75)
Duration of MV (hours)	22.83 (18.57–39.92)
ICU LOS (days)	4 (3–5)
Hospital LOS (days)	30 (25–43)

Table 1 (continued)

Data are presented as n (%), mean ± standard deviation, or median (interquartile range). ADL, Activities of Daily Living; NRS-2002, Nutrition Risk Screening 2002; APACHE II, Acute Physiology and Chronic Health Evaluation II; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; ICU, intensive care unit; LOS, length of stay.

Table 2 Reasons for unplanned early rehospitalization following initial discharge after lung transplantation stratified by presenting symptoms (n=29)

Presenting symptom	N [%]
Chest distress with shortness of breath	11 [38]
Cough with expectoration	6 [21]
Fever	6 [21]
Anorexia	2 [7]
Palpitation	1 [3]
Hyperpotassemia (blood test during follow-up)	1 [3]
Excessive tacrolimus concentration (blood test during follow-up)	1 [3]
Hypercapnia (blood test during follow-up)	1 [3]

coronary atherothrombotic disease (P=0.09), and albumin concentration (P=0.055). Multivariate logistic regression revealed that patients with a longer duration of postoperative MV [odds ratio (OR) =1.027; 95% confidence interval (CI): 1.008–1.046; P=0.004] and a higher NRS-2002 score (OR =1.615; 95% CI: 1.189–2.194; P=0.002) were more likely to experience UER (*Table 4*).

Discussion

To our knowledge, this is the first study to investigate UER in lung transplant recipients in China. This is also the first study on the influence of preoperative nutritional risk status on UER. Our primary findings were as follows: (I) the incidence of UER in China was similar with that of

Table 3 Univariate analysis of lung transplant patients who did and did not experience unplanned early rehospitalization (n=99)

Characteristics	No readmission	Readmission	P value
Patients	70 (70.7)	29 (29.3)	
Demographic characteristics			
Male	64 (91.4)	24 (82.8)	0.37†
Age			0.054†
<60 years	46 (65.7)	13 (44.8)	
≥60 years	24 (34.3)	16 (55.2)	
Education			0.07†
Elementary school and below	20 (28.6)	7 (24.1)	
Junior high school	14 (20.0)	11 (37.9)	
Senior high school	15 (21.4)	1 (3.4)	
College degree or above	21 (30.0)	10 (34.5)	
Marital status			0.68†
Married	66 (94.4)	29 (100.0)	
Single	3 (4.3)	0 (0.0)	
Divorced/widowed	1 (1.4)	0 (0.0)	
Diagnosis			0.30†
Restrictive disease	44 (62.9)	19 (65.5)	
Obstructive disease	20 (28.6)	5 (17.2)	
Other	6 (8.6)	5 (17.2)	
Preoperative condition			
Body mass index			0.28†
<18.5 kg/m^2	26 (37.1)	6 (20.7)	
18.5–23.9 kg/m^2	26 (37.1)	15 (51.7)	
≥24 kg/m^2	18 (25.7)	8 (27.6)	
Diabetes mellitus	6 (8.6)	4 (13.8)	0.68†
Hypertension	7 (10.0)	3 (10.3)	>0.99†
Coronary atherothrombotic disease	21 (30.0)	4 (13.8)	0.09†
Epstein-Barr virus infection	9 (12.9)	5 (17.2)	0.80†
Albumin (g/L)	36.5±3.9	34.7±5.1	0.055‡
Hemoglobin (g/L)	135.4±17.5	132.4±24.5	0.50‡
ADL			0.90†
≥60	59 (84.3)	26 (89.7)	
40–59	5 (7.1)	1 (3.4)	
<40	6 (8.6)	2 (6.9)	
NRS-2002	1.9±1.7	3.1±1.4	0.001§
APACHE II	7.3±2.8	9.2±2.8	0.003‡

Table 3 *(continued)*

Table 3 *(continued)*

Characteristics	No readmission	Readmission	P value
Surgery-related characteristics			
Urgent lung transplantation	3 (4.3)	1 (3.4)	>0.99†
Bilateral transplant	32 (45.7)	15 (51.7)	0.59†
Duration of surgery (hours)	4.8±1.2	5.1±1.3	0.19‡
Postoperative condition			
Duration of ECMO support (hours)	15.1±14.3	29.1±31.6	0.02§
Duration of MV (hours)	28.5±19.2	47.5±40.7	0.01§
ICU LOS			0.02†
≤4 days	53 (75.7)	15 (51.7)	
>4 days	17(24.3)	14 (48.3)	
Hospital LOS			0.04†
≤30 days	40 (57.1)	10 (34.5)	
>30 days	30 (42.9)	19 (65.5)	

Data are presented as n (%), mean ± standard deviation. †, Chi-squared test; ‡, Student's *t*-test; §, Mann-Whitney *U* test. ADL, Activities of Daily Living; NRS-2002, Nutrition Risk Screening 2002; APACHE II, Acute Physiology and Chronic Health Evaluation II; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; ICU, intensive care unit; LOS, length of stay.

Table 4 Multivariate analysis of lung transplant recipients who did and did not experience unplanned early rehospitalization (n=99)

Variables	β	SE	Wald χ^2	P	OR (95% CI)
Postoperative MV duration	0.027	0.009	8.144	0.004	1.027 (1.008, 1.046)
Preoperative NRS-2002 score	0.479	0.156	9.402	0.002	1.615 (1.189, 2.194)

β, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; MV, mechanical ventilation; NRS-2002, Nutrition Risk Screening 2002.

American; (II) chest distress with shortness of breath, cough with expectoration, and fever were the three most common reasons for UER; and (III) for the first time, we found that the preoperative NRS-2002 score and postoperative MV duration were risk predictors of UER.

The reported incidence of UER within 30 days after initial discharge in lung transplant recipients ranges from 29.8–45.4% in America (3-8). In our study, this percentage was 29.3%, which is similar with that reported previously. This result indicated that UER is also a prominent problem for lung transplant patients in China.

The main reasons for UER according to presenting symptoms, from high incidence to low incidence, were chest distress with shortness of breath, cough with expectoration, fever, anorexia and palpitation. Three patients were scheduled for emergency hospitalization due to hyperkalemia, increased tacrolimus concentration, or hypercapnia during routine outpatient follow-up. In Mollberg *et al.*'s study (5), rehospitalization after LT was mainly related to pulmonary complications (59%), followed by gastrointestinal (18%), cardiac (5%), metabolic (2.5%) and neurologic complications (2.5%). In Lushaj *et al.*'s study (4), the most common cause of readmission was infection, which accounted for 33% of the readmissions, and respiratory tract infections accounted for the majority of infections. In that study, respiratory adverse events were defined as a series of clinical manifestations, including tachypnea, respiratory failure, pleural effusion, and anastomotic stenosis, which were also the main reasons for early readmission within 30 days after discharge. In our study, we stratified the cause of UER according to patient complaints and presenting symptoms. Chest distress with shortness of breath, cough with expectoration, and fever were strongly related to infection and respiratory adverse events, which can be considered early warning symptoms. This result indicated that when a patient has these abnormal manifestations, we should be aware of the potential occurrence of UER and prepare in advance.

In the study by Alrawashdeh *et al.* (8), MV duration was statistically analyzed as a categorical variable (<48 *vs.* 48 hours), and the findings showed that MV duration had no effect on the UER. This method of data processing may lead to missing useful information. In our study, we analyzed MV duration as a continuous variable and found for the first time that a longer MV duration was associated with a greater risk of UER (OR =1.027; 95% CI: 1.008–1.046; P=0.004). Although the odds ratio was low, the MV duration in this study was statistically analyzed in hours, not in days. If the MV duration was extended for 6 hours, the risk of UER would increase by 16.2%. Over time, if the MV duration was extended for 1 day, the risk of UER would increase by 64.8%. Therefore, the clinical relevance of MV duration in predicting UER remains valuable. In clinical practice, the judge of optimal timing of extubation varies among different physicians. Patients may have objectively met the extubation conditions, but for caution, some physicians may choose to extend the MV duration to further observe whether the transplanted lung function is truly stable. Such clinical decision-making is not uncommon in practice. Our findings suggested that early extubation as soon as the condition allows may provide more benefit to patients, which was also consistent with an international consensus (13) recommendations for early extubation in the ICU in the absence of graft dysfunction. Thus, the impact of the prolonged MV duration on UER deserves more attention from clinicians, and more effort is needed to advance the implementation of early extubation strategies.

However, although we demonstrated a correlation between MV duration and UER, we still cannot ignore another possibility. After lung transplantation, if postoperative complications such as primary graft dysfunction and diaphragm dysfunction occur, the lung function will not be able to perform normally, which will lead to an extension of MV duration (14,15). Thus, it seems plausible that MV duration could be a secondary marker for other factors—such as postoperative complications or suboptimal recovery of lung function—rather than a primary predictor of UER. We should explore this possibility in greater depth and consider how MV duration may be intertwined with other variables. Unfortunately, owing to the inherent limitations of the retrospective design, relevant information was not recorded in detail or measured comprehensively. Moreover, due to the limitation of sample size, the overall number of complications may not be sufficient to meet the requirements of statistical analysis. In the future, we will expand the sample size to further reveal the role of MV duration in the occurrence of UER through a prospective study design.

Nutritional status is strongly related to the survival rate and complications of lung transplant recipients (16). Lung transplant recipients have a greater incidence of nutritional risk and malnutrition, which seriously affects their short-term prognosis (17). The European Society of Parenteral and Enteral Nutrition (ESPEN) recommends the NRS-2002 as the preferred screening tool for nutritional risk, and patients with an NRS-2002 score of 3 or higher are considered at nutritional risk (18). In Ding *et al.*'s study (17), patients with preoperative NRS-2002 scores ≥3 had higher drainage volumes, longer hospitalization times, and higher total hospitalization costs than those with NRS-2002 scores <3. In our study, we found a positive correlation between the NRS-2002 score and the risk of UER in lung transplant recipients (OR =1.615; 95% CI: 1.189–2.194; P=0.002). This finding further validated the important impact of nutritional risk on the prognosis of lung transplant recipients. In addition, the high OR value also increased the attention degree to the nutritional risk management. During the waiting period, adequate nutritional support should be actively provided to improve physical status and promote postoperative recovery, thus reducing the likelihood of developing UER.

Albumin is the most important protein in human plasma and can reflect nutritional status. In this study, there was no statistical evidence that preoperative albumin concentration was predictive of UER, which is consistent with Mollberg *et al.*'s findings (5). In our lung transplant center, if the albumin concentration is less than 30 g/L, intravenous albumin is routinely administered to maintain a concentration within the normal range. The data we collected were the most recent albumin values before surgery, which may be the reason for the lack of statistical significance of the results of this study. In future research, we can analyze the effect of albumin concentration on the day of admission on UER because it is more representative of the true nutritional status of the patient.

Early after LT, acute respiratory failure may occur for various reasons, including primary graft dysfunction, acute cardiac insufficiency in patients with pulmonary arterial hypertension, infection, acute rejection, manifested by hypoxemia, acidosis, increased pulmonary artery pressure, and decreased pulmonary compliance (19). All of these conditions require a delay in ECMO removal. Therefore, the timing of ECMO removal is a complicated clinical decision-making process that requires adequate assessment of the patient's specific situation. All patients included in this study received ECMO support during transplantation. After transfer to the ICU, ECMO was removed under the premise of stable respiratory and circulation function. However, our study was unable to demonstrate whether the duration of postoperative ECMO support impacts the UER. This finding suggests that the strategy of early removal of ECMO is not feasible, unlike the strategy of early extubation. The optimization of critical care management should be considered from more perspectives rather than through the excessive pursuit of "early removal".

There are several limitations to our study. First, the retrospective design introduced inherent limitations such as potential selection bias and an inability to control for unmeasured confounders. Second, the data was obtained from the EMRS, and some information was inaccessible because of unrecorded or unmeasured, for example, complications related to prolonged MV duration, such as primary graft dysfunction and diaphragm dysfunction. Third, the data collection focused on the period of preoperative and intensive care. The results can only provide a reference for preoperative care and postoperative intensive care, and the long-term risk factors after surgery need to be further investigated in the future. Fourth, the study was limited by its single-center, retrospective design and was conducted at one transplant center in China. While this provided valuable insights into lung transplant outcomes in a specific population, the generalizability of the findings to other centers, especially those outside of China, was limited. In future studies, a multi-center approach could enhance the external validity of our results.

Conclusions

The incidence of unplanned rehospitalization within 30 days after the initial discharge of lung transplant recipients is common in China. Providing adequate nutritional support to reduce nutritional risk during the waiting period and implementing early extubation during intensive care can promote the rapid recovery of LT patients and reduce the risk of UER after discharge. It is essential to strengthen the monitoring of clinical signs after surgery. The identification of early-warning symptoms of UER can help patients take advanced measures to reduce harm. Future efforts will be directed toward the accurate identification of high-risk patients. A multi-center, prospective cohort study is needed to further elucidate the risk factors for UER in lung transplant recipients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1302/rc

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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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethical Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (No. 2023-0862). Written informed consent was waived by the ethics committee due to the anonymized retrospective nature of the analysis.

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