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Relevance of superoxide dismutase type 1 to lipoid pneumonia: the first retrospective case-control study

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Abstract

Background Lipoid pneumonia (LP) is a rare disease caused by the accumulation of lipids and lipid-laden macrophages in the alveoli inducing damage. LP is difficult to differentiate from other similar diseases without pathological evidence, such as upper respiratory tract infection (URTI), pneumonia, cryptogenic organizing pneumonia (COP), pulmonary alveolar proteinosis (PAP), lung mucinous adenocarcinoma and pulmonary edema. Given the high misdiagnosis rate and limited statistical clinical and treatment data, there is an urgent need for novel indicators of LP. Superoxide dismutase type1 (SOD1) plays an essential role in macrophage polarization, promoting inflammation and oxidative stress, but its association with LP remains unknown.

Methods The clinical data of 22 patients with proven LP from January 2008 to June 2024 and their prognostic information up to June 2024 were retrospectively gathered (ClinicalTrials.gov, NCT06430008). Additionally, information on patients with URTI, bacterial and fungal pneumonia, COP, PAP, lung mucinous adenocarcinoma and pulmonary edema, was collected totaling 140 patients as control subjects. Receiver operating characteristic curve, machine learning (ML), regression and survival analyses were performed to analyze the data.

Results In multivariate regression analysis, the sole independent risk factor of LP was the level of SOD1 (OR 0.922, 95% CI: 0.878 ~ 0.967, $P < 0.001$), while smoking status (β= -0.177, 95% CI -18.645~-2.836, $P = 0.008$), diabetes mellitus (β= -0.191, 95% CI: -20.442~-3.592, $P = 0.005$), and total sialic acid (TSA) (β= -0.426, 95% CI: -0.915~ -0.433, $P < 0.001$) independently influenced the level of SOD1. SOD1 had the highest importance score in ML-based LP predictive models. Additionally, advanced age may be associated with higher mortality in LP.

Conclusion SOD1 is a potential biomarker for LP, but the smoking status, diabetes comorbidities, and TSA level need to be considered.

Keywords Lipoid pneumonia, Superoxide dismutase type1, Total sialic acid, Machine learning, Rare disease

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Introduction

Lipoid pneumonia (LP) is a rare lung disease first discovered by Laughlin in 1925 [1], since then, however, no accurate epidemiological data have been reported for determining its morbidity [2, 3]. LP can be triggered by the accumulation of various lipids (exogenous and endogenous) in the lung, where they are further phagocytosed by macrophages, resulting in a series of inflammatory reactions and injuries. Exogenous LP is triggered by the inhalation of lipid-containing substances, including mineral oil [4–6], while the endogenous LP results from the release of fats and cholesterol in response to tissue damage from a variety of causes [7].

Samhouri BF et al. examined 34 patients with LP at Mayo Medical Center from 1998 ~ 2020 to ascertain a clinical description and reveal that LP may be asymptomatic and may not always exhibit fatty attenuation on chest CT, instead paving pattern, mosaic attenuation, ground–glass opacities or consolidative opacities [8]. However, other than this study, there is currently no clinical research on LP, and only case series.

The diagnosis of LP currently depends on a unique history of lipid exposure and pathologic manifestations (large numbers of lipid-laden macrophages on lung biopsy or bronchoalveolar lavage (BAL) samples staining positively for Oil Red O or Sudan III) [9]; however, without employing pathologic tests, its difficult to distinguish LP from other diseases, such as cryptogenic organizing pneumonitis (COP), pulmonary alveolar proteinosis (PAP), lung infections (bacterial pneumonia, fungal pneumonia), pulmonary edema, and mucinous adenocarcinoma (MA) of the lung. Furthermore, treatment is limited to the removal of the responsible lipid exposure, glucocorticoid administration, and lung lavage [10]. Additionally, the prognosis depends on the etiology and the timing of the diagnosis; thus, novel indicators are urgently needed to facilitate early diagnosis and treatment [11].

Although lung histopathology can reveal lipid-laden macrophages, the underlying molecular mechanism hasn't yet been elucidated for lacking of research, and we speculate that macrophages may be activated and elicit a series of responses related to oxidative stress after the phagocytosis of lipids in the development of LP.

Superoxide dismutase (SOD) is a type of antioxidant metalloenzyme present in mammals in forms such as Cu/Zn-SOD (SOD1), Mn-SOD (SOD2), and Fe-SOD (SOD3). SOD1 can be detected in human serum with a pivotal role in the oxidative and antioxidant balance of the organism. It's also inextricably associated with the onset and progression of many diseases, such as neurological disorders [12]. It reported that SOD1 was positively correlated with disease severity in patients with community-acquired pneumonia [13]. Brajesh Singh et al. detected decreased SOD1 in the plasma of patients with COVID-19 [14]. Total sialic acid (TSA), an N-acetylated derivative of neuraminic acid, may be associated with macrophage activation, owing to the expression of sialic acid receptors on its surface [15, 16].

Therefore, in this retrospective study, we aimd to investigate the relationship between SOD1 and LP and further explore whether SOD1 can be utilized as a specific indicator.

Methods

Patients and eligibility criteria

This was a single-center retrospective case-control study. 26 patients were with LP from January 2008 to June 2024, 22 of whom with pathology or positive lipid staining were included in the descriptive study, and 20 of whom tested for SOD1 and TSA on admission were included in the case-control study as the case group, matched 1:1 from the 7 control groups (patients with upper respiratory tract inflammation (URTI), bacterial pneumonia, fungal pneumonia, COP, PAP, pulmonary edema, and MA of the lung) on age and sex, so there were 20 patients with LP in the case group and 140 patients tested for SOD1 and TSA on admission in the control groups. Among them, bacterial and fungal pneumonia needed to be confirmed with pathogen evidence; COP, PAP, and MA of the lung required definite histopathological evidence; the patients with pulmonary edema were those with interstitial changes (thickening of the interlobular septa, crazy paving) on chest CT that were primarily caused by heart failure. Patients with possible LP but only a history of inhalation of lipids unsupported by pathology or positive lipid staining, as well as underage and pregnant patients, were excluded. The study flow chart is illustrated in Fig. 1.

Clinical data collection

All patient's information was manually reviewed. We gathered data on gender, age, smoking status, comorbidities, pulmonary function, chest CT, diagnostic and therapeutic methods, white blood cell (WBC) count, the neutrophil–lymphocyte ratio (NLR), the lymphocyte–monocyte ratio (LMR), the levels of C-reactive protein (CRP), SOD1 and TSA on admission, and follow-up data for patients with LP, including symptoms, oxygenation status, survival, and the most recent chest CT findings up to June 2024.

Study outcomes

The primary outcome of the study was the level of SOD1 in LP patients and controls and their value for diagnostic or prognostic predictor of LP, and the secondary outcome was the level of TSA and all-cause mortality during hospitalization or follow-up.

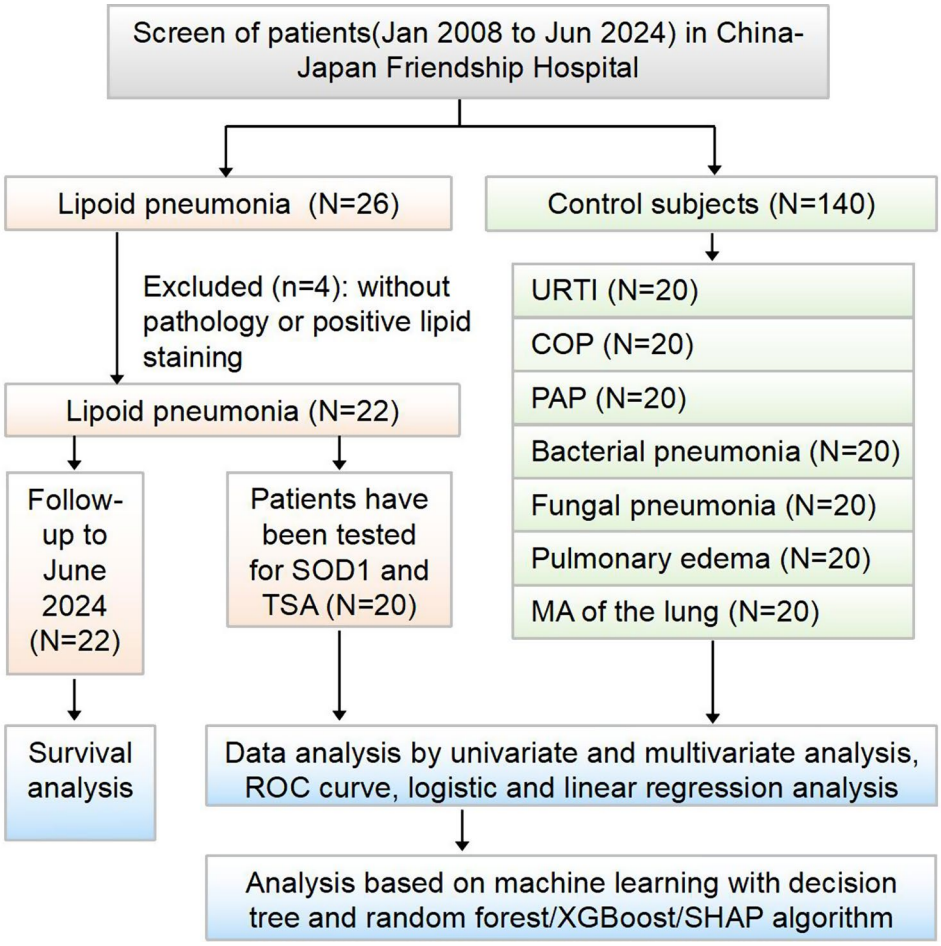

Fig. 1 Flowchart of the study design. SOD1 = superoxide dismutase type 1; TSA = total sialic acid; URTI = upper respiratory tract infection; COP = cryptogenic organizing pneumonia; PAP = pulmonary alveolar proteinosis; MA = mucinous adenocarcinoma; ROC = receiver operating characteristic; SHAP = SHapley Additive exPlanations

The measurement of SOD1 and TSA levels

The serum SOD1 concentrations (U/mL) were measured through the SOD1 assay by using colorimetry measurement by qualified laboratory physicians. And the levels of TSA (mg/dl) were measured by enzyme assays by qualified laboratory physicians. Both the levels of SOD1 and TSA were measured on admission of the patients.

Statistical analysis

Continuous variables are manifested as the means with standard deviations (SDs) if normally distributed, or medians with interquartile ranges if nonnormally distributed. Categorical variables are presented as frequency rates and percentages. Normally distributed continuous variables were analyzed by the *t* test or analysis of variance (ANOVA) and the nonnormally with nonparametric tests. Categorical data were analyzed with the chi-square test or Fisher's exact test. We also applied receiver operating characteristic (ROC) curve analysis, survival analysis and logistic and linear regression analyses reported as odds ratios (ORs) with 95% confidence intervals (CIs). SPSS version 27.0, GraphPad Prism, MedCalc and R were used. PASS version 2021 and MedCalc were used for sample size calculation, the α value was set as 0.05, the power was set as 0.9, and the ROC curve analysis needs 19 cases for every group, the regression analyses needs at least 17 cases every group, and as for the survival analysis needs at least 32 cases every group. A one-vs.-rest strategy was employed for subgroup and interaction analysis. Machine learning (ML) algorithms including decision tree, random forest, eXtreme Gradient Boosting (XGBoost) and SHapley Additive exPlanations (SHAP) were used to optimize a diagnostic model and determine the importance of identified risk factors. The sample size was estimated with MedCalc. We considered a two-sided $P < 0.05$ to indicate statistical significance.

Clinical trial registration information

This study was approved by the Ethics Committee of the China-Japan Friendship Hospital on May 16, 2024. The

Table 1 Demographic data of the patients with lipoid pneumonia (*N* = 22)

Characteristic	LP
Sex, N(%)	
Male	10 (45.45%)
Female	12 (54.55%)
Age, y (median, IQR 25-75%)	63 (39,81)
Smoking status, N(%)	
Yes	3 (13.64%)
No	19 (86.36%)
Chest CT scan findings (*N* = 22)	
Ground-glass opacities	
Unilateral	2 (9.09%)
Bilateral	12 (54.55%)
Not present	8 (36.36%)
Consolidative opacities	
Unilateral	7 (31.82%)
Bilateral	10 (45.45%)
Not present	5 (22.73%)
Nodules	2 (9.09%)
Fatty attenuation	1 (4.55%)
Crazy-paving	3 (13.64%)
mosaic	1 (4.55%)
Distribution of CT scan findings	
Bilateral	7 (31.82%)
Bilateral lower lobes with or without other lobes	11 (50.00%)
Single lobe	4 (18.18%)
Method of diagnosis	
Lung biopsy	16 (72.73%)
TBLB	5 (22.73%)
TBCB	3 (13.64%)
CT scan-guided needle lung biopsy	6 (27.27%)
Ultrasound-guided needle lung biopsy	1 (4.55%)
Lobectomy	1 (4.55%)
BAL	6 (27.27%)
Culprit substance	
Paraffin oil	14 (63.64%)
Essential oil	1 (4.55%)
Gasoline	2 (9.09%)
Coal tar	1 (4.55%)
Diesel oil	2 (9.09%)
Endogenous	2 (9.09%)
Pulmonary function test	
FVC, (% of predicted), *N* = 10	72.58 ± 20.12
FEV_1, (% of predicted), *N* = 10	74 ± 20.68
FEV_1/FVC, *N* = 10	86.12 ± 7.88
TLC, (% of predicted), *N* = 8	73.19 ± 16.96
DLCO, (% of predicted), *N* = 8	56.86 ± 14.96

LP = lipoid pneumonia; DLCO = lung diffusing capacity of carbon monoxide; TBLB = transbronchial lung biopsy; TBCB = transbronchial cryobiopsy; BAL = bronchoalveolar lavage; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; TLC = total lung capacity; IQR = interquartile range

study protocol was designed and conducted in accordance with the Declaration of Helsinki under ethical number 2024-KY-144 and registered with ClinicalTrail.gov (NCT06430008) on May 28, 2024.

Results

Clinical characteristics

Among the 22 patients with LP, ten were male, and the median age at diagnosis was 57 years. 86.36% of the patients were nonsmokers. Sixteen patients were diagnosed according to the pathological results of lung biopsies (large numbers of lipid-laden macrophages on lung biopsy), and the other six according to the BAL (BAL samples staining positively for Oil Red O or Sudan III). Furthermore, twenty patients had exogenous LP, and two had endogenous. The chest CT findings mostly consisted of consolidative opacities. Pulmonary function tests were performed only in ten patients, and seven patients presented with obstruction while five demonstrated a restrictive pattern. Only eight patients completed the total lung capacity (TLC) and lung diffusing capacity of carbon monoxide (DLCO) tests;, six had diffusion impairment (Table 1).

Next, we compared the data from the 20 patients with LP with admission SOD1 levels with those from the control group. No differences were observed in age, gender, smoking status, or comorbidities. Comparison of the WBC count, NLR, LMR, CRP, SOD1, and TSA levels among the 8 groups revealed significant differences in the WBC count ($P = 0.002$), level of CRP ($P < 0.001$), NLR ($P < 0.001$), level of SOD1 ($P < 0.001$), and level of TSA ($P < 0.001$) after adjustment of p value. (Table 2, e-Table 1).

The WBC count, CRP, NLR, SOD1 and TSA levels of each group are presented in Fig. 2. The WBC count was significantly higher in patients with LP than in those with URTI (Fig. 2A). The levels of CRP and NLR were significantly greater in patients with LP than URTI, PAP, COP and MA of the lung (Fig. 2B and C). The level of SOD1 in the LP group were significantly lower than in those with URTI, PAP, COP, bacterial pneumonia, fungal pneumonia, pulmonary edema, and MA of the lung groups (Fig. 2D). And compared with other groups, the TSA levels of the patients with LP were markedly elevated (Fig. 2E).

The ROC curves

To better apply our findings to clinical diagnosis, we performed ROC curve analysis. A SOD1 level of 134 U/ml was the optimal cutoff point for differentiating URTI

Table 2 Demographic data and clinical characteristics of all the subjects

Characteristic	Case	Control (*N* = 140)							*P* value
	LP (*N* = 20)	URTI (*N* = 20)	PAP (*N* = 20)	COP (*N* = 20)	Bacterial pneumonia (*N* = 20)	Fungal pneumonia (*N* = 20)	Pulmonary edema (*N* = 20)	MA of the lung (*N* = 20)	
Sex, N (%)									0.959
Male	8 (40.00%)	11 (55.00%)	10 (50.00%)	8 (40.00%)	9 (45.00%)	10 (50.00%)	11 (55.00%)	11 (55.00%)	
Female	12 (60.00%)	9 (45.00%)	10 (50.00%)	12 (60.00%)	11 (55.00%)	10 (50.00%)	9 (45.00%)	9 (45.00%)	
Age, years (median, 25-75%)	64 (43–75)	58 (39–65)	51 (39–59)	55 (46–61)	61 (56–70)	66 (47–66)	65 (47–78)	61 (55–67)	0.052
Smoking status, N (%)									0.335
Yes	2 (10.00%)	6 (30.00%)	5 (25.00%)	5 (25.00%)	4 (20.00%)	9 (45.00%)	7 (35.00%)	7 (35.00%)	
No	18 (90.00%)	14 (70.00%)	15 (75.00%)	15 (75.00%)	16 (80.00%)	11 (55.00%)	13 (65.00%)	13 (65.00%)	
Comorbidities[a], N (%)									
Bronchiectasis	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (15.00%)	2 (10.00%)	0 (0.00%)	0.089
Pulmonary emphysema	2 (10.00%)	1 (5.00%)	0 (0.00%)	1 (5.00%)	0 (0.00%)	3 (15.00%)	3 (15.00%)	1 (5.00%)	0.41
Hypertension	7 (35.00%)	8 (40.00%)	5 (25.00%)	10 (50.00%)	7 (35.00%)	7 (35.00%)	15 (75.00%)	7 (35.00%)	0.063
CAD	4 (20.00%)	2 (10.00%)	1 (5.00%)	1 (5.00%)	1 (5.00%)	2 (10.00%)	6 (30.00%)	4 (20.00%)	0.206
DM	8 (40.00%)	5 (25.00%)	1 (5.00%)	6 (30.00%)	5 (25.00%)	4 (20.00%)	9 (45.00%)	3 (15.00%)	0.097
Tumor	6 (30.00%)	2 (10.00%)	1 (5.00%)	2 (10.00%)	4 (20.00%)	2 (10.00%)	4 (20.00%)	/	0.376
GERD	2 (10.00%)	4 (20.00%)	1 (5.00%)	0 (0.00%)	2 (10.00%)	0 (0.00%)	3 (15.00%)	5 (25.00%)	0.084
Cholecystolithiasis	2 (10.00%)	1 (5.00%)	0 (0.00%)	1 (5.00%)	1 (5.00%)	2 (10.00%)	2 (10.00%)	2 (10.00%)	0.935
Gastrointestinal bleeding	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)	1 (5.00%)	1 (5.00%)	0 (0.00%)	> 0.999
Parkinson's Disease	1 (5.00%)	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (10.00%)	0 (0.00%)	0 (0.00%)	0.574
Stroke	4 (20.00%)	2 (10.00%)	1 (5.00%)	1 (5.00%)	3 (15.00%)	3 (15.00%)	6 (30.00%)	2 (10.00%)	0.394
Hematologic tests									
WBC×10^9/L (median, 25-75%)	8.25 (6.26–10.62)	5.35(4.61–6.51)	6.44(5.98–8.73)	6.14(5.11–8.05)	8.18(5.74–11.10)	7.15(4.76–9.76)	8.89(6.67–10.58)	6.25(5.40–7.49)	0.002
CRP (mg/l) (median, 25-75%)	50.50 (8.25–154.10)	2.50(2.50–4.38)	2.750(2.50–4.30)	2.50(2.19–6.36)	12.73(3.49–43.49)	3.82(2.50-20.27)	35.17(2.68–72.71)	2.50(2.50–4.41)	< 0.001
NLR (median, 25-75%)	6.24(3.82–8.63)	1.97(1.13–2.43)	2.15(1.78–3.59)	2.05(1.61–3.01)	4.31(2.45–6.87)	2.94(1.89–6.32)	7.03(3.33-15.00)	2.25(1.59–3.94)	< 0.001
LMR (median, 25-75%)	3.59(1.98–5.63)	4.64(3.62–5.08)	4.20(2.77–4.73)	3.71(2.70–5.01)	2.72(2.03–4.64)	3.08(1.92-5,23)	2.81(1.80–4.95)	3.21(2.42–4.44)	0.085
SOD1 (U/ml) (mean ± SD)	114.10 ± 22.65	164.20 ± 11.31	164.30 ± 26.75	153.50 ± 16.12	154.30 ± 19.51	160.70 ± 16.84	160.70 ± 44.30	152.70 ± 11.80	< 0.001
TSA (mg/dl) (median, 25-75%)	93.50 (68.25–104.50)	51.00(46.25–55.75)	51.00(46.25–64.75)	57.50(50.25–65.5)	61.50(56.00-64.75)	51.00(47.50-62.25)	59.50(51.25–71.50)	56.50(49.00–69.00)	< 0.001

[a]Some patients had more than one comorbidity. LP = lipoid pneumonia; SOD1 = superoxide dismutase type 1; TSA = total sialic acid; URTI = upper respiratory tract infection; COP = cryptogenic organizing pneumonia; PAP = pulmonary alveolar proteinosis; MA = mucinous adenocarcinoma; SD = standard deviation; WBC = white blood cell; CRP = C-reactive protein; NLR = neutrophil-lymphocyte ratio; LMR = lymphocyte-monocyte ratio; GERD = gastroesophageal reflux disease; DM = diabetes mellitus; CAD = coronary artery disease

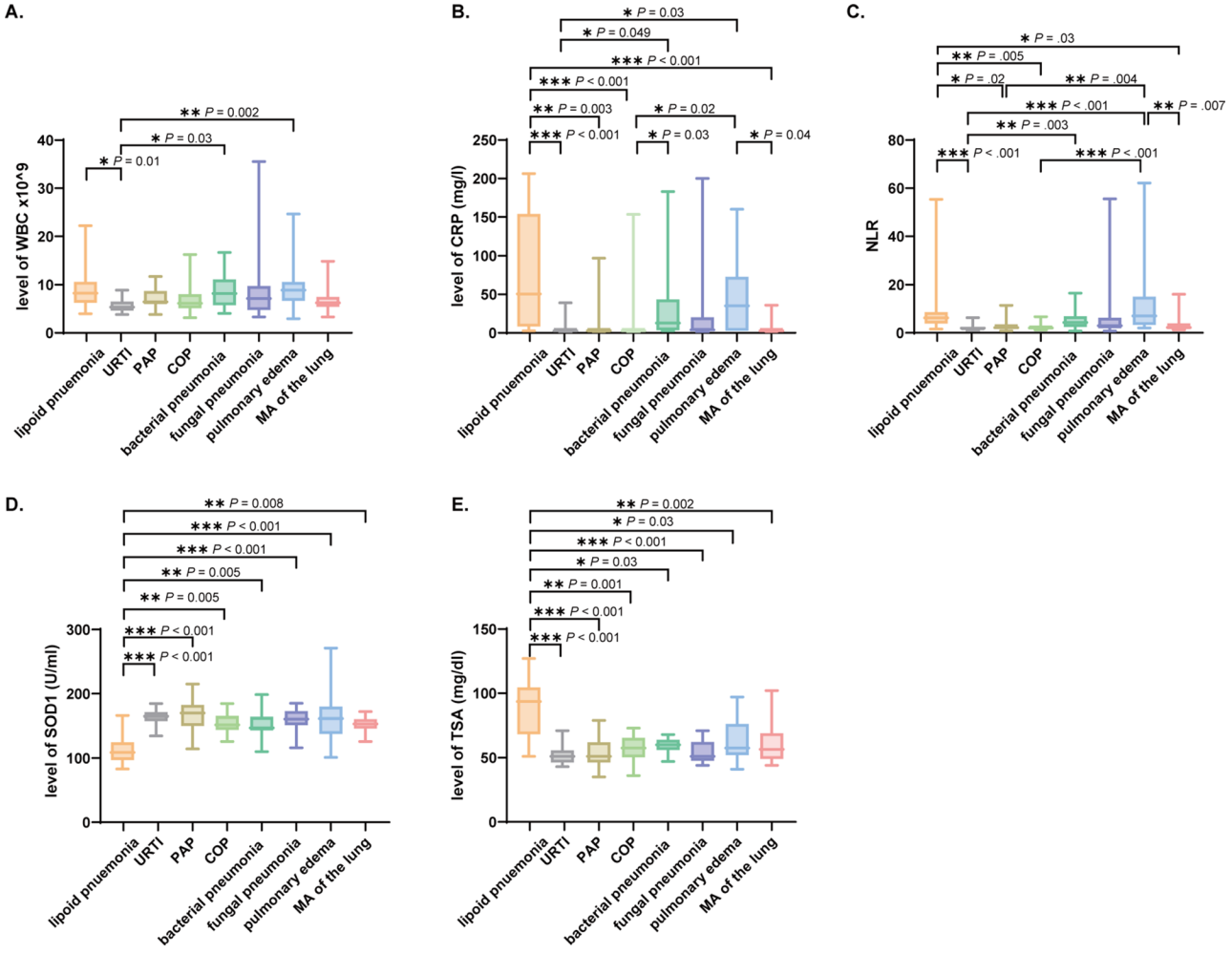

Fig. 2 Differences in WBC count, CRP level, NLR, SOD1 level and TSA level among URTI, LP, PAP, COP, bacterial and fungal pneumonia, MA of the lung and pulmonary edema patients: (**A**) Comparison of WBC count among different diseases. (**B**) Comparison of the levels of CRP among different diseases. (**C**) Comparison of the NLR among different diseases. (**D**) Comparison of the SOD1 level among different diseases. (**E**) Comparison of the TSA level among different diseases. The Kruskal-Wallis test was applied to multiple comparisions with the corrected *P* value using Dunn's test. LP = lipoid pneumonia; WBC = white blood cell; CRP = C-reactive protein; NLR = neutrophil–lymphocyte ratio

from LP patients, with an area under the curve (AUC) value of 0.958 and a 95% CI of 0.842 ~ 0.996, resulting in a sensitivity of 85% and specificity of 100%; more importantly, the AUC value for SOD1 was the highest among and significantly different from those for bacterial pneumonia, fungal pneumonia, and pulmonary edema (Fig. 3A). For differentiating from URTI, a level of TSA of 56 U/ml was the best cutoff point, with the highest AUC value of 0.969, 95% CI of 0.859 ~ 0.999, sensitivity of 100% and specificity of 80% (Fig. 3B). We also analyzed the WBC (AUC = 0.825, 95% CI: 0.672 ~ 0.927, Fig. 3C), CRP (AUC = 0.873, 95% CI: 0.729 ~ 0.957, Fig. 3D), and NLR (AUC = 0.920, 95% CI 0.789 ~ 0.982, Fig. 3E) in differentiating LP from URTI; additionally, except for the CRP between the patients with LP and fungal pneumonia ($P = 0.0243$), the remaining were not statistically significantly different from bacterial pneumonia, fungal pneumonia or pulmonary edema. When the one-vs.-rest strategy was employed, a level of SOD1 of 125.3 U/ml was the optimal cutoff point for differentiating patients in the LP group from the non-LP, with an AUC of 0.911, 95% CI of 0.856 ~ 0.950, sensitivity of 80%, and specificity of 94.29%, while the TSA level of 66 mg/dl (AUC: 0.902, 95% CI: 0.845 ~ 0.943, sensitivity: 85%, specificity: 83.57%) was the optimal cutoff point for differentiating LP patients from the non-LP (Fig. 3F). The AUC value for the combination of SOD1 and TSA level was 0.944, with a 95% CI of 0.896 ~ 0.974, a sensitivity of 85% and a specificity of 93.57% (Fig. 3F).

Prognosis of patients with LP

We next summarized the data on the follow-up of 22 patients with LP, who had a median follow-up time of 40.5 months. Thirteen patients (59.09%) showed

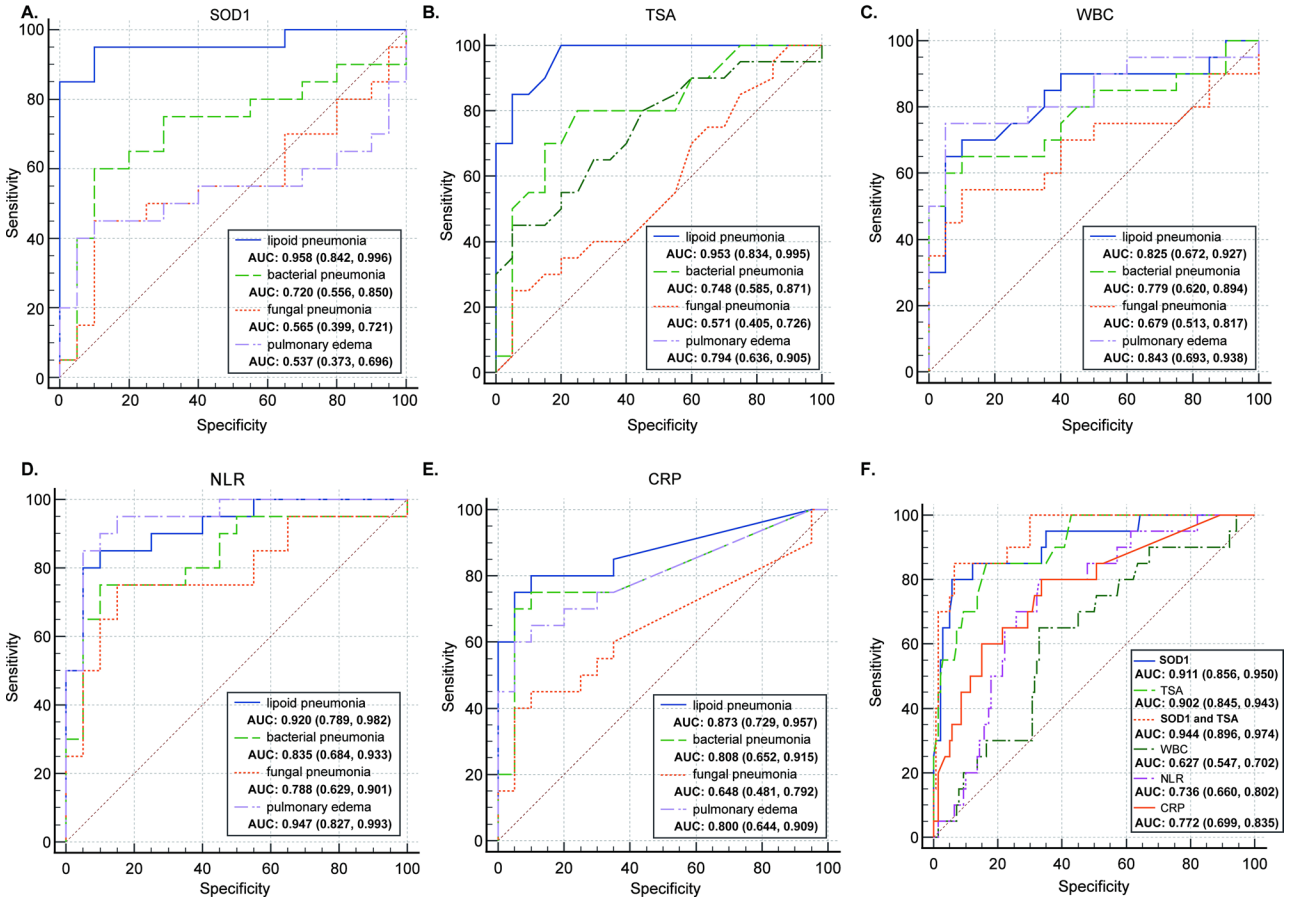

Fig. 3 ROC curve analysis for SOD1 level, TSA level, WBC count, NLR, and CRP level in patients with URTI, LP, bacterial pneumonia, fungal pneumonia and pulmonary edema: (**A**) ROC curve for the levels of SOD1. (**B**) ROC curve for the levels of TSA. (**C**) ROC curve for WBC count. (**D**) ROC curve for the NLR. (**E**) ROC curve for the levels of CRP. (**F**) ROC curves for SOD1, TSA, WBC, NLR and CRP in the LP versus non-LP groups with the one-vs.-rest strategy

Table 3 Follow-up data

Variable	Data
Clinical follow-up data	
Improved	13 (59.09%)
Stable	4 (18.18%)
Worsened	5 (22.73%)
Need for long-term oxygen therapy	6 (27.27%)
Death	5 (22.73%)
Treatment	
Corticosteroids, *N* = 18 (81.82%)	
Death	5 (27.78%)
Lung lavage, *N* = 6 (27.27%)	
Whole lung lavage, *N* = 4 (18.18%)	
Sequential lavage of segments or lobes, *N* = 2 (9.09%)	
Death	2 (33.33%)
SOD1 > 125.3 U/ml, *N* = 4	
Death	0 (0.00%)
SOD1 < = 125.3,*N* = 16	
Death	5 (25.00%)

SOD1 = superoxide dismutase type 1

improvements, five (22.73%) worsened (including death), and six (27.27%) still required continuous oxygenation as of the last follow-up date. Eighteen patients (81.82%) were treated with corticosteroids, and of these, 5 died because of myocardial infartion (1, 20%) and resporatory failure (4, 80%); lung lavage therapy was applied to 6 (27.27%) patients, and of these, 2 (33.33%) died (Table 3); however, there was no significant difference in the mortality rate according to survival analysis (Figure E1A). More interestingly, we noted that the deceased patients were older ($P = 0.036$, Fig. 4A), and when patients grouped by median age, survival analysis revealed a significant difference in both short-term ($P = 0.016$) and long-term ($P = 0.040$) outcomes (Fig. 4B). There were no differences in SOD1 (Fig. 4C) or TSA level (Figure E1C) between the deceased and surviving patients, and no differences in survival analyses grouped by cutoff point of SOD1 (125.3 U/ml) from the ROC analysis (Figure E1B).

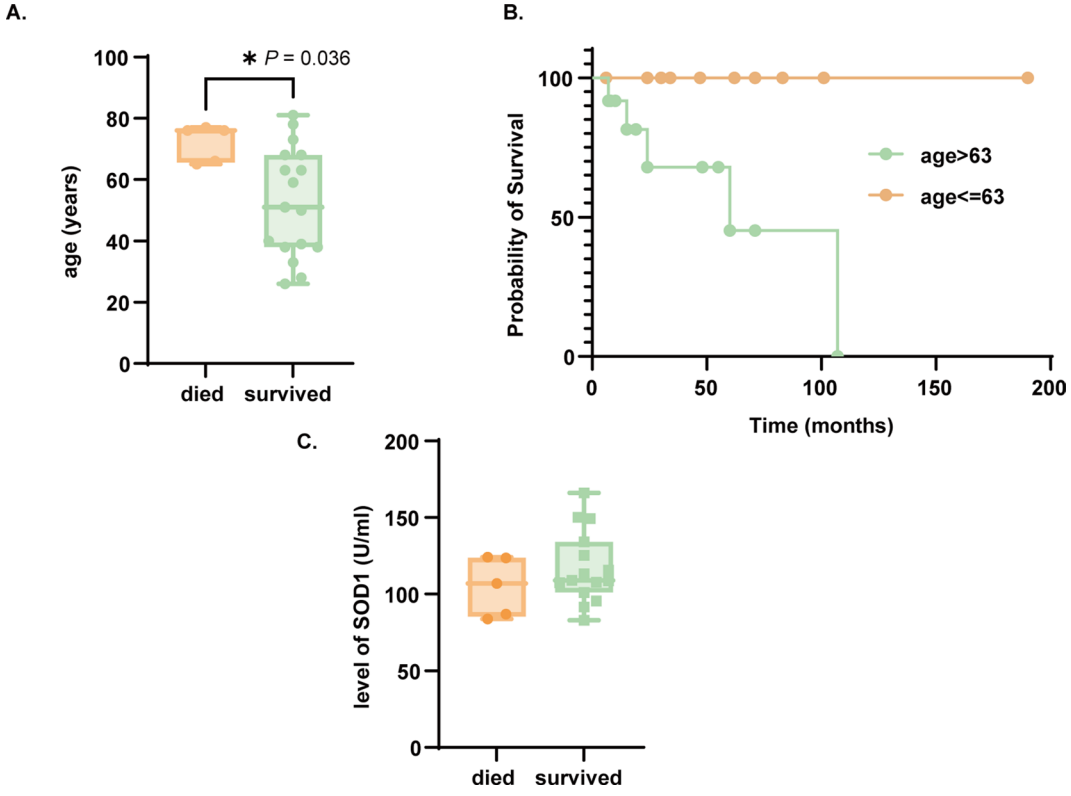

Fig. 4 Analysis of the outcomes of patients with lipoid pneumonia: (**A**) Box plot demonstrating the age distributions of the deceased and surviving groups; (**B**) Survival analysis after grouping according to the median age (63 years) of patients with lipoid pneumonia ($N = 22$); (**C**) Box plot demonstrating the levels of SOD1 in the deceased and surviving groups

SOD1 is correlated with LP

We analyzed possible variables associated with LP with univariate multinomial logistic regression, including WBC, CRP, NLR, SOD1, and TSA (Table 4). Subsequent multivariate multinomial regression analysis revealed that the level of SOD1 was an independent risk factor, with lower levels of SOD1 more likely in patients with LP (OR 0.922, 95% CI: 0.878 ~ 0.967, $P < 0.001$; Table 4). There was no multicollinearity among the variables.

SOD1-related factors

Univariate regression analysis revealed that smoking status, diabetes mellitus (DM), stroke, CRP, and TSA were associated with SOD1, and multivariate linear regression analysis revealed that smoking status (β=-0.177, 95% CI: -18.645~-2.836, $P = 0.008$), DM (β=-0.191, 95% CI: -20.442~-3.592, $P = 0.005$) and the level of TSA (β=-0.426, 95% CI: -0.915~-0.433, $P < 0.001$) were independently associated with the level of SOD1 (Table 5). With a Durbin Watson test of 1.722, the data were consistent with independence and the conditions for normality according to residual analysis. There was no multicollinearity among the independent variables.

Subgroup and interaction analyses

In an attempt to clarify the stability of the regression model, we performed subgroup and interaction analyses with forest plots in R software, stratifying patients by smoking status, DM, stroke, TSA, CRP, and WBC on the basis of the cutoff points from ROC curve analysis. The analysis indicated no interaction among the above mentioned factors (Fig. 5).

ML-based predictive model for LP

Based on the above data, we applied a one-vs.-rest strategy to classify the cases into LP and non-LP for ML model analysis based on decision tree, random forest, XGBoost and SHAP algorithms by R. We allocated 80%

Table 4 Factors associated with LP

Variable	β	*P* value	OR (95%)	Adjust β	Adjust *P* value	Adjust OR (95%CI)
Sex						
Male	-0.606	0.344	0.545 (0.155, 1.914)			
Female						
Age	0.038	0.100	1.039 (0.993, 1.086)			
Smoke						
Yes	-1.350	0.130	0.259 (0.045,1.486)			
No						
Comorbidities						
Pulmonary emphysema	-0.747	0.556	0.474 (0.039,5.688)			
Hypertension	0.214	0.744	1.238 (0.343, 4.464)			
CAD	-0.811	0.384	0.444 (0.072, 2.760)			
DM	-0.693	0.315	0.500 (0.130, 1.930)			
Tumor	-1.350	0.130	0.259 (0.045, 1.486)			
GERD	0.811	0.384	2.250 (0.362,13.971)			
Cholecystolithiasis	-0.747	0.556	0.474 (0.039,5.688)			
Gastrointestinal bleeding						
Parkinson's Disease	0.000	1.000	1.000 (0.058,17.181)			
Stroke	-0.811	0.384	0.444 (0.072, 2.760)			
Hematologic tests						
WBC×10^9/L	0.506	0.001	1.658 (1.220, 2.254)	0.367	0.098	1.444 (0.934,2.231)
CRP(mg/l)	0.072	0.028	1.074 (1.008, 1.145)	0.019	0.491	1.019 (0.965,1.077)
NLR	0.850	0.001	2.340 (1.400, 3.910)	0.416	0.135	1.515 (0.879,2.613)
LMR	-0.143	0.343	0.867 (0.646,1.164)			
SOD1(U/ml)	-0.097	< 0.001	0.907 (0.874, 0.941)	-0.082	< 0.001	0.922 (0.878,0.967)
TSA(mg/dl)	0.166	< 0.001	1.180 (1.102, 1.264)	0.098	0.051	1.089 (1.000,1.185)

LP = lipoid pneumonia; SOD1 = superoxide dismutase type 1; TSA = total sialic acid; WBC = white blood cell; CRP = C-reactive protein; NLR = neutrophil-lymphocyte ratio; LMR = lymphocyte-monocyte ratio; GERD = gastroesophageal reflux disease; DM = diabetes mellitus; CAD = coronary artery disease; OR = odd ratio; CI = confidence interval

of the data to the training set and 20% to the test set to generate the decision tree model plot (Fig. 6A). The model predicted a probability of possible LP of 70% when the SOD1 was greater than or equal to 125.5 U/ml and of 92% if meanwhile the level of TSA greater than 68.5 mg/ml, for an overall accuracy of 0.844. With the application of the XGBoost, the tree model with the highest output gain and var values, as demonstrated in Fig. 6B, had an accuracy is 0.875. The importance of each factor was analyzed with the random forest (Fig. 6C-D). Validation of the XGBoost model via SHAP revealed that SOD1 contributed the most to the predictive effects of the model and that lower levels of SOD1 were more indicative of a diagnosis of LP (Fig. 6E, F).

Discussion

In this study, we analyzed data from patients with LP, URTI, PAP, COP, bacterial pneumonia, fungal pneumonia, pulmonary edema, and MA of the lung; explored new diagnostic strategies of LP; and discovered that the level of SOD1 of patients on admission is an independent risk factor of LP diagnosis. Furthermore, we found that smoking status, DM and TSA could affect the levels of SOD1. We also constructed a decision tree model for LP and verified the importance of SOD1, demonstrating the prospect of employing this potential biomarker in clinical practice. The overall of the study was shown in the Fig 7.

The chest CT scans of patients with LP mostly revealed consolidative opacities and ground-glass opacities; the paving pattern was uncommon, which is similar to what was described in a previous study [8], but unlike that study, fatty attenuation was observed in only 1 patient in our study. The pulmonary function profiles of the patients are also similar to those in the above report. In terms of comorbidities, unlike most case reports [17], few comorbidities, such as stroke and GERD, were observed in our study.

Table 5 Factors associated with SOD1

Variable	β	95%CI	*P* value	Adjust β	Adjust 95%CI	Adjust *P* value
Sex	-0.085	-13.305, 3.923	0.284			
Male						
Female						
Age	-0.147	-0.579, 0.016	0.064			
Smoke	-0.178	-20.370, -1.454	0.024	-0.177	-18.645, -2.836	0.008
Yes						
No						
Comorbidities[a], N (%)						
Bronchiectasis	-0.018	-25.310, 20.177	0.824			
Pulmonary emphysema	0.003	-16.699, 17.459	0.965			
Hypertension	-0.128	-15.849, 1.565	0.107			
CAD	-0.081	-19.316, 6.197	0.311			
DM	-0.176	-20.858, -1.370	0.026	-0.191	-20.442, -3.592	0.005
Tumor	-0.116	-23.096, 4.132	0.171			
GERD	0.068	-7.945, 20.038	0.395			
Cholecystolithiasis	0.011	-15.878, 18.279	0.890			
Gastrointestinal bleeding	0.120	-6.339, 48.622	0.131			
Parkinson's Disease	-0.001	-27.846, 27.514	0.991			
Stroke	-0.219	-29.701, -5.209	0.005	-0.082	-17.344, 4.239	0.232
Hematologic tests						
WBC(×10^9/L)	-0.055	-1.390, 0.669	0.491			
CRP(mg/l)	-0.343	-0.277, -0.110	< 0.001	-0.130	-0.159, 0.013	0.094
NLR	-0.146	-0.976, 0.031	0.066			
LMR	0.072	-1.200, 3.223	0.368			
TSA (mg/dl)	-0.507	-1.017, -0.588	< 0.001	-0.426	-0.915, -0.433	< 0.001

SOD1 = superoxide dismutase type 1; TSA = total sialic acid; WBC = white blood cell; CRP = C-reactive protein; NLR = neutrophil-lymphocyte ratio; LMR = lymphocyte-monocyte ratio; GERD = gastroesophageal reflux disease; DM = diabetes mellitus; CAD = coronary artery disease; OR = odd ratio; CI = confidence interval

The level of SOD1 was lower in deceased patients (over 63 years old) with no significant difference which may because the sample size is not enough, and we also observed a trend toward better outcomes for patients who did not receive corticosteroids or undergo lung lavage, probably because the disease itself was milder in this group. Due to the limited number of patients, it is not possible to conduct a statistical analysis to determine which treatment decision can significantly reduce the mortality rate of patients. As shown in Table 3, the mortality rates of various treatments do not seem to be significantly different, but it can be found that no deaths occurred in LP patients with SOD1 higher than 125.3 U/ml. Therefore, LP patients aged over 63 and with low level of SOD1 may have a poor prognosis and need to be diagnosed as early as possible.

Both the regression and ML analyses indicated SOD1 was closely related to the diagnosis of LP. Recently it has been suggested that mutations in SOD1 are associated with clinical outcomes in amyotrophic lateral sclerosis [18], and in mouse model, knocking down *SOD1* causes mitochondrial dysfunction inducing shortened lifespans [19]. In addition, SOD1 has been suggested to play an important role in Parkinson's disease [19], and elevated levels of SOD1 are closely associated with cancer [20, 21]. We suspected that the decrease in the level of SOD1 in LP patients is related to macrophage oxidative stress and the imbalance in immune regulation, and to a certain extent, it reveals the possible role of macrophages and immune-related mechanisms in LP. But unfortunately, there has been no animal model of LP that allows us to further investigate the mechanisms, and whether *SOD1*

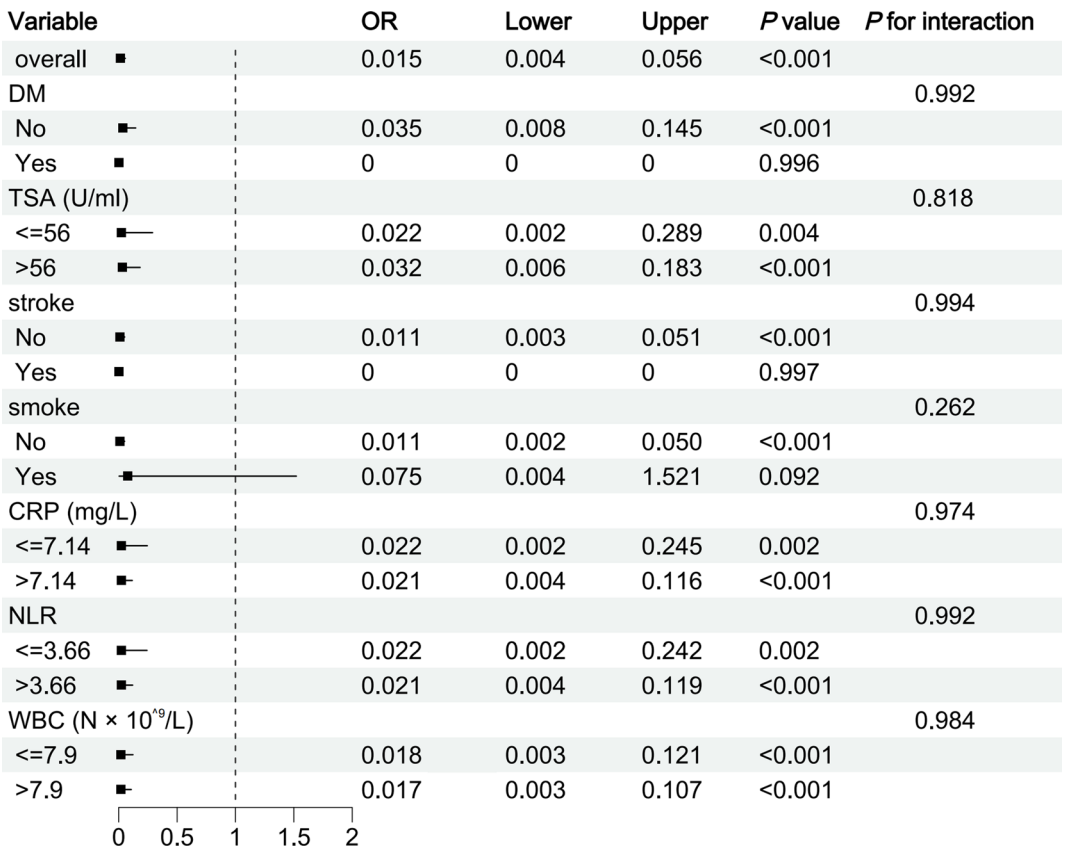

Fig. 5 Subgroup and interaction analyses are presented with forest plots for all groups. The odd ratios are presented as black squares, and black horizontal lines represent the 95% confidence intervals (CIs) of each group

with a common mutation in LP requires larger-scale investigation. Since there are no other studies on markers of LP, and there is no known markers of LP for SOD1 to refer to for comparison, this made our study to be the first study to discover a marker for this rare disease.

We also discovered that smoking status, DM, and TSA were correlated with the SOD1 level; similar findings were observed to suggest that smokers had higher levels of SOD1 [22], while DM were more likely to have lower levels of SOD1 [23, 24].

For the first time, we indicated that elevated levels of TSA were associated with lower levels of SOD1 in LP. TSA is found in various tissues and plays key role in cell–cell communication and infections. TSA is also identified as a broad-spectrum tumor marker but lacks specificity [25]. Yu-Mei Mi et al. revealed positive correlation between the TSA and complement C3 level in children with *Mycoplasma pneumoniae* infections [26]; in our analysis, we noticed that although the level of TSA wasn't an independent risk factor for LP, it demonstrated a high AUC in ROC curve analysis and was especially effective in differentiating LP when analyzed in conjunction with SOD1; More importantly, it was the second-most important factor of LP in our ML analysis, and both decision tree models included TSA as the second node. Therefore, further studies with larger sample sizes may better demonstrate the role of TSA in the diagnosis of LP. And we speculate that it is possible that the decrease in SOD1 levels accompanied by the increase in TSA binds to the receptors on the surface of macrophages and further activates macrophages to induce damage, and whether there is an interaction between SOD1 and TSA or whether

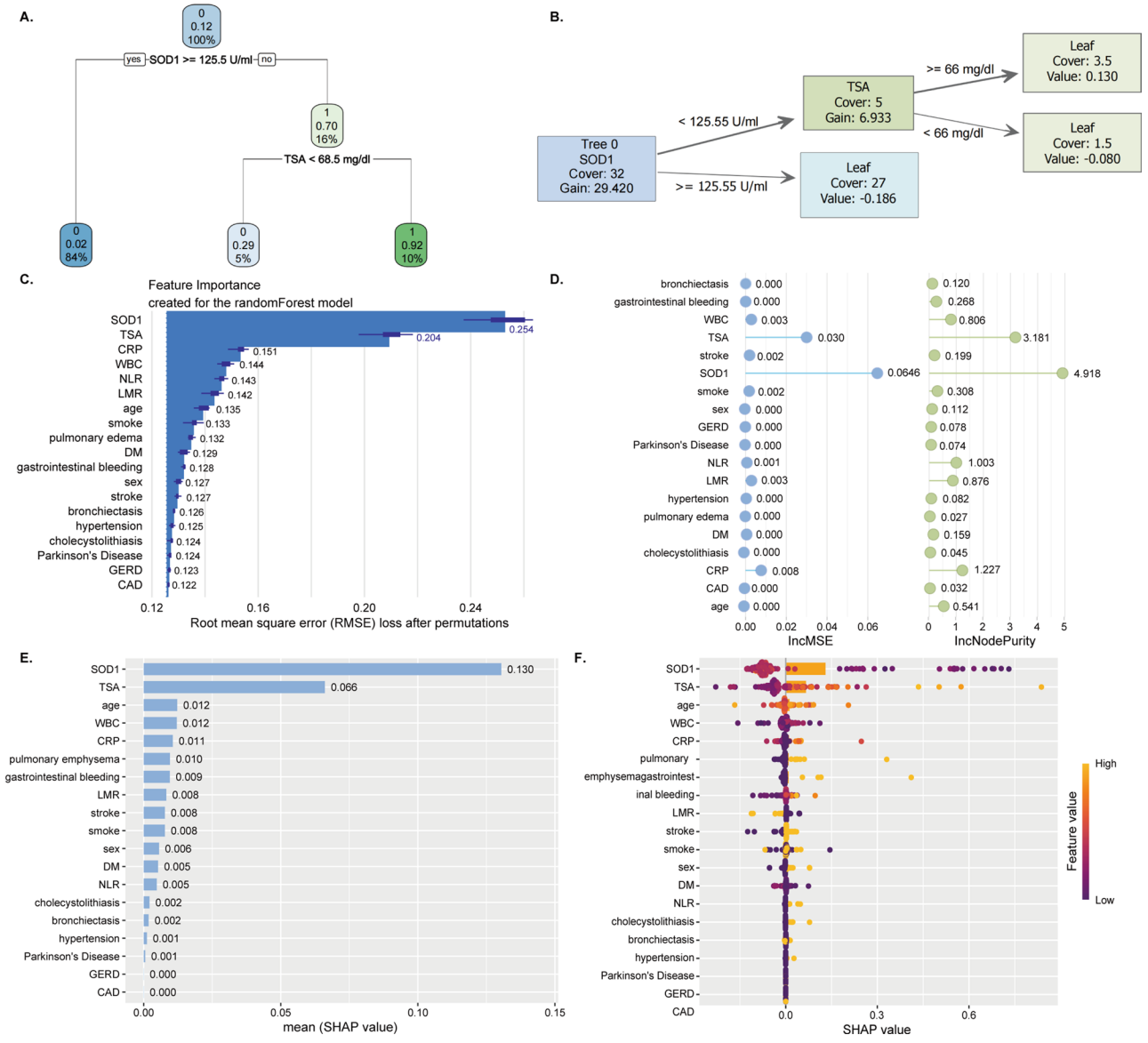

Fig. 6 Machine learning-based analysis of lipoid pneumonia: (**A**) Decision tree model plot; (**B**) Tree model with application of the XGBoost algorithm; (**C**) Importance of each factor according to random forest analysis; (**D**) IncMSE and IncNodePurity of each factor according to random forest analysis; (**E**) Feature importance in the XGBoost model according to SHAP analysis. (**F**) SHAP values for all patients in the XGBoost model; SHAP = SHapley Additive exPlanations; XGBoost = eXtreme Gradient Boosting

there is an upstream and downstream relationship, the further research is needed.

Our study has several limitations, firstly, a relatively small number of cases (despite meeting the minima derived from power analysis of 19 cases for ROC curve analysis, but not 32 for survival analysis), thus, the results may not be very reliable. In the future, a multicenter study and larger number of cases may yield more accurate results. Secondly, this study may have a selection bias because we did not include other diseases that needed to be identified such as sarcoidosis and other types of lung tumors, and there was a lack in the degree of case representation. Thirdly, less than half of the patients completed the pulmonary function tests, notably affecting some of the analyses, however, fortunately, none of our LP patients were lost to follow-up. Lastly, numerous algorithms for ML are constantly being updated [27, 28], so in this study, we utilized the most recent and popular algorithms to maximize model accuracy [29–31]; however, these algorithms suffer from over-fitting and the relatively small amount of data available for training. Nevertheless, the excellent performance of the SOD1 in our developed model is promising.

In conclusion, we conducted the first retrospective case-control study of LP and discovered that the level of SOD1 is an independent risk factor of the disease, which

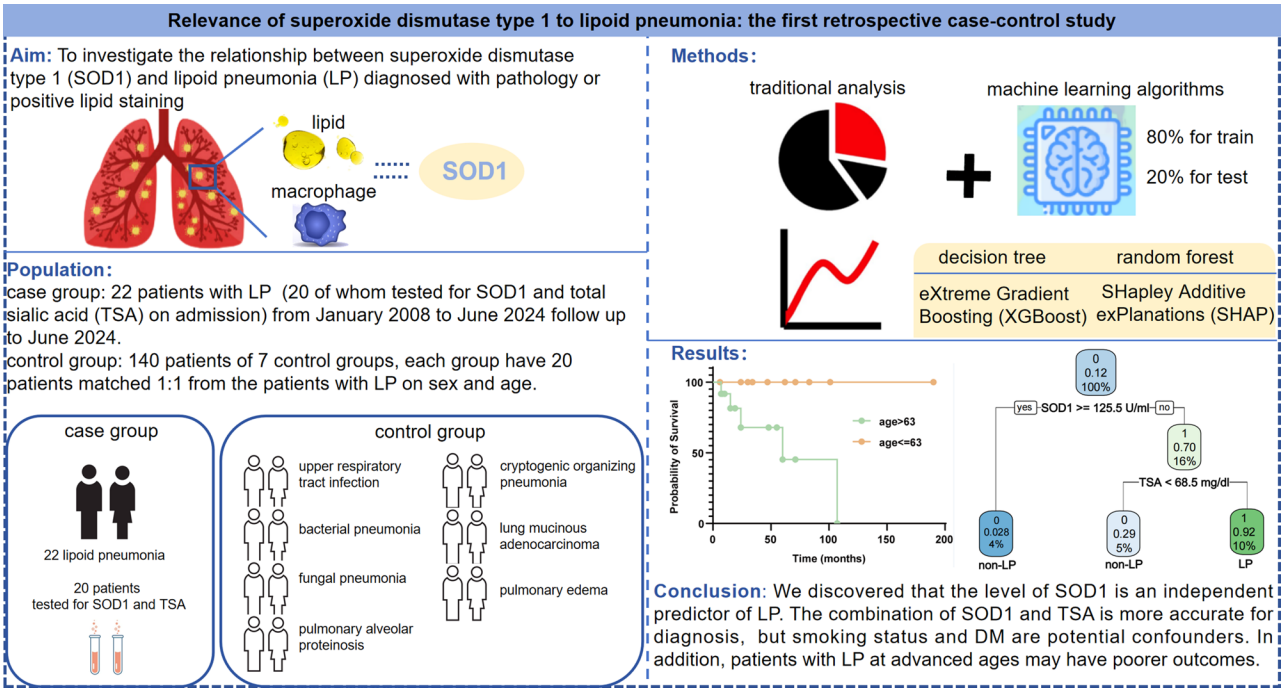

Fig. 7 A overall of the study. We analyzed data from patients with LP, URTI, PAP, COP, bacterial pneumonia, fungal pneumonia, pulmonary edema, and MA of the lung; explored new diagnostic strategies of LP; and discovered that the level of SOD1 of patients on admission is an independent risk factor of LP diagnosis. We also constructed a decision tree model for LP and verified the importance of SOD1, demonstrating the prospect of employing this potential biomarker in clinical practice

was confirmed by regression analysis and ML methods. The combination of SOD1 and TSA is more accurate for differentiating LP than either index alone; however, smoking status, DM are potential confounders. In addition, patients with LP at advanced ages may have poorer outcomes, hence worth more medical attention. The above results will have certain clinical application value and assist clinical diagnosis and prognosis judgment.

Abbreviations

LP	Lipoid pneumonia
SOD1	Superoxide dismutase type 1
TSA	Total sialic acid
URTI	Upper respiratory tract infection
COP	Cryptogenic organizing pneumonia
PAP	Pulmonary alveolar proteinosis
MA	Mucinous adenocarcinoma
WBC	White blood cell
CRP	C-reactive protein
NLR	Neutrophil–lymphocyte ratio
LMR	Lymphocyte–monocyte ratio
SD	Standard deviation
IQR	Interquartile range
ANOVA	Analysis of variance
ML	Machine learning
OR	Odds ratio
CI	Confidence interval
ROC	Receiver operating characteristic
AUC	Area under the curve
XGBoost	eXtreme Gradient Boosting
SHAP	SHapley Additive exPlanations
TLC	Total lung capacity
DLCO	Lung diffusing capacity of carbon monoxide
GERD	Gastroesophageal reflux disease
DM	Diabetes mellitus
CAD	Coronary artery disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-025-03101-3.

Supplementary Material 1: Figure E1. Analysis of the outcomes of patients with lipoid pneumonia: (A) Survival analysis after grouping according to treatment strategy; (B) Survival analysis after grouping according to SOD1 level (125.3 U/ml); (C) Box plot demonstrating the levels of TSA in the deceased and surviving groups

Supplementary Material 2

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Author contributions

H.Y.N. and is the guarantor of the content of the manuscript, including the data and analysis. D.H.P., R.Y.H., and H.Y.N. designed the study. H.Y.N., H.Y.Z. and L.Z. analyzed the data. H.Y.N. and R.Y.H. wrote the initial draft of the manuscript. D.H.P. reviewed the manuscript. M.W.Q., Q.Y.H., L.Z. and L.M.Y. gathered the data. All the authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethical approval
This study was approved by the Ethics Committee of the China-Japan Friendship Hospital on May 16, 2024. The study protocol was designed and conducted in accordance with the Declaration of Helsinki under ethical number 2024-KY-144 and registered with ClinicalTrail. gov (NCT06430008) on May 28, 2024.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Schwaiblmair M, Berghaus T, Haeckel T, et al. [Lipoid pneumonia - an underestimated syndrome]. Dtsch Med Wochenschr. 2010;135(1–2):27–31.
2. Rana D, Kaushik N, Sadhu S, et al. Idiopathic lipoid pneumonia: an incidental finding in autopsy specimen. Autops Case Rep. 2020;10(1):e2020143.
3. Ikehara K, Suzuki M, Tsuburai T, et al. Lipoid Pneumonia Lancet. 2002;359(9314):1300.
4. Gonzalez CS, Arrieta NP, Gorospe SL. Exogenous lipoid pneumonia secondary to chronic paraffin oil consumption. Med Clin (Barc). 2023;160(4):186.
5. Yamada A, Kagawa T, Nishimoto Y, et al. Exogenous lipoid pneumonia caused by gargling with Sesame Oil: a Case Report. J Thorac Imaging. 2022;37(6):W97–100.
6. Brancaleone P, Delefortrie Q, Descamps O, et al. Lipoid Pneumonia Associated with Polyethylene Glycol Chronic Aspiration. Am J Respir Crit Care Med. 2023;207(8):e71–2.
7. Chieng HC, Ibrahim A, Chong WH, et al. Lipoid Pneumonia Am J Med Sci. 2022;363(5):452–5.
8. Samhouri BF, Tandon YK, Hartman TE, et al. Presenting clinicoradiologic features, causes, and clinical course of exogenous lipoid pneumonia in adults. Chest. 2021;160(2):624–32.
9. Marco DN, Martinez D, Salgado E, et al. Lipoid pneumonia after a suicide attempt with detergent ingestion. Intensive Care Med. 2023;49(10):1247–8.
10. Shang L, Gu X, Du S, et al. The efficacy and safety of therapeutic lung lavage for exogenous lipoid pneumonia: a systematic review. Clin Respir J. 2021;15(2):134–46.
11. Beck LR, Landsberg D. Lipoid Pneumonia. 2023.
12. Xu J, Su X, Burley SK et al. Nuclear SOD1 in Growth Control, oxidative stress response, amyotrophic lateral sclerosis, and Cancer. Antioxid (Basel). 2022;11(2).
13. Xie G, Cheng J, Liu Y et al. Serum SOD1 level predicts the severity and prognosis of community-acquired pneumonia patients. Am J Med Sci. 2024;368(4):311–319.
14. Singh B, Singh S, Bhatia JK, et al. Role of Matrix Degradation, oxidative stress, inflammation & Trace Elements in COVID-19 patients: a Multivariate Study from India. Indian J Clin Biochem. 2023;38(2):193–203.
15. Cavalcante T, Medeiros MM, Mule SN, et al. The role of sialic acids in the establishment of infections by pathogens, with Special Focus on Leishmania. Front Cell Infect Microbiol. 2021;11:671913.
16. Munday J, Floyd H, Crocker PR. Sialic acid binding receptors (siglecs) expressed by macrophages. J Leukoc Biol. 1999;66(5):705–11.
17. Boutros J, Muzzone M, Benzaquen J, et al. A case report of exogenous lipoid pneumonia associated with avocado/soybean unsaponifiables. BMC Pulm Med. 2019;19(1):234.
18. Berdynski M, Miszta P, Safranow K, et al. SOD1 mutations associated with amyotrophic lateral sclerosis analysis of variant severity. Sci Rep. 2022;12(1):103.
19. Park JH, Elpers C, Reunert J, et al. SOD1 deficiency: a novel syndrome distinct from amyotrophic lateral sclerosis. Brain. 2019;142(8):2230–7.
20. Li X, Chen Y, Zhao J, et al. The specific inhibition of SOD1 selectively promotes apoptosis of Cancer cells via regulation of the ROS Signaling Network. Oxid Med Cell Longev. 2019;2019:9706792.
21. Eleutherio E, Silva MR, de Araujo BA, et al. SOD1, more than just an antioxidant. Arch Biochem Biophys. 2021;697:108701.
22. Puiu L, Petrovan A, Felicia G et al. Possible relationship between smoking, plasma copper/zinc (Cu/Zn)-Superoxide dismutase (SOD1) levels and cardiovascular risk. June 2012. Conference: Romanian National Conference of Pneumology, 2012At: POIANA BRASOV. https://www.researchgate.net/publication/288268691.
23. Nithya K, Angeline T, Isabel W, et al. SOD1 gene + 35A/C (exon3/intron3) polymorphism in type 2 diabetes Mellitus among South Indian Population. Genet Res Int. 2016;2016:3787268.
24. Muscogiuri G, Salmon AB, Aguayo-Mazzucato C, et al. Genetic disruption of SOD1 gene causes glucose intolerance and impairs beta-cell function. Diabetes. 2013;62(12):4201–7.
25. Zhou X, Yang G, Guan F. Biological functions and Analytical strategies of sialic acids in Tumor. Cells. 2020;9(2).
26. Mi YM, Qi Q, Zhang L, et al. Assessment of serum sialic acid correlated with C3 in children with Mycoplasma pneumoniae pneumonia. J Clin Lab Anal. 2020;34(3):e23078.
27. Li Y, Wu X, Yang P, et al. Machine learning for Lung Cancer diagnosis, treatment, and prognosis. Genomics Proteom Bioinf. 2022;20(5):850–66.
28. van den Bosch T, Warps AK, de Neree TBM, et al. Predictors of 30-Day mortality among Dutch patients undergoing colorectal Cancer surgery, 2011–2016. JAMA Netw Open. 2021;4(4):e217737.
29. Khera R, Haimovich J, Hurley NC, et al. Use of Machine Learning models to predict death after Acute myocardial infarction. JAMA Cardiol. 2021;6(6):633–41.
30. Antony B, Blau H, Casiraghi E, et al. Predictive models of long COVID. EBioMedicine. 2023;96:104777.
31. Shao J, Feng J, Li J et al. Novel tools for early diagnosis and precision treatment based on artificial intelligence. Chin Med J Pulmonary Crit Care Med. 2023;(3):148–60.

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