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Article

Cohort Profile: Zhuhai Microplastics Exposure Cohort (Z-MEC), a Hospital-Based Prospective Cohort of Patients with Respiratory Diseases

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Abstract: Increasing evidences have indicated a human internal exposure of Microplastics (MPs), whereas epidemiological evidence linking MPs to health outcomes remains limited, especially from prospective cohort studies. We established the Zhuhai Microplastics Exposure Cohort (Z-MEC), a hospital-based prospective cohort of 700 patients with respiratory diseases between October 2020 and November 2022. Apart from blood and urine sampling, bronchoalveolar lavage fluid (BALF) of patients undergoing bronchoscopy was further collected to evaluate MPs burden using both the laser direct infrared (LDIR) and scanning electron microscopy. Clinical data, laboratory indices, and questionnaire information were also obtained at baseline, and repeatedly collected during the scheduled follow-up according to the individual medical care. Among 479 participants with BALF, the detection rate of total MPs reached 96.12%, with a median abundance of 115.02 (IQR, 34.77–303.43) particles per gram of BALF. The most prevalent polymers included polyethylene (PE), high-density polyethylene (HDPE), polyurethane (PU), and polyvinyl chloride (PVC). Detailed morphological analysis revealed that inhaled MPs are typically irregular in shape, and larger-sized particles have been found deep within the lungs. In summary, the ongoing Z-MEC study serves as a vital platform for research on MPs exposure assessment and their potential health impacts.

Keywords: microplastics; cohort study; bronchoalveolar lavage fluid; respiratory disease; shape parameter; LDIR

1. Introduction

Over the past decade, microplastics (MPs) have emerged as a pervasive environmental pollutant, raising global concern due to their ubiquity and potential for biological invasion. Defined as synthetic polymer particles less than 5 mm in diameter [1], microplastics originate from two primary sources: the direct release of industrially produced particles (e.g., cosmetic beads and industrial abrasives) and the secondary fragmentation of larger plastic debris through physical, chemical, and photo-degradative processes [2,3]. With global plastic production reaching 407 million tons annually as of 2015, the environmental accumulation of microplastics has accelerated dramatically, and the cumulative mass of plastic waste in landfills or the natural environment is projected to soar to 12,000 million metric tons without significant intervention by 2050 [4]. Consequently, these particles have been detected across all

environmental compartments, including marine and freshwater systems, soils, and the atmosphere [1]. This escalating environmental contamination has recently translated into direct evidence of human internal exposure, with microplastics being detected across a growing spectrum of biological matrices (such as lung, liver, placenta, brain, feces, blood, breast milk, etc.) [5–9]. The extensive detection has indeed prompted profound public concern about the potential health risks posed by microplastics. However, the risk assessment of microplastics is encountering significant challenges, including limitations in detection methodology and the lack of evidence from cross-temporal cohort studies [10]; as a result, our understanding of microplastic toxicity is still in its infancy.

Studies have suggested that microplastics enter the human body mainly through pathways such as the food chain or airborne transmission [1]. Unlike those ingested through the digestive tract, the inhaled microplastics are more likely to deposit within the respiratory system, even deeper into the distal lung [9,11]; their physicochemical characteristics render them resistant to clearance mechanisms, accumulate over time, and exert persistent local effects, thereby posing greater potential toxicity [12,13]. Emerging experimental evidence suggests cause for concern. In vitro and in vivo studies have demonstrated that microplastic exposure induces oxidative stress, mitochondrial dysfunction, inflammatory cytokine release, and cellular apoptosis in pulmonary epithelial models [14,15]. More recently, epidemiological investigations have begun to link the microplastics burden with clinical respiratory endpoints. A notable cross-sectional study of patients with community-acquired pneumonia found that higher microplastic concentrations in respiratory samples were significantly associated with disease severity, accompanied by alterations in respiratory microbiota and inflammatory profiles [16]. Yet, the magnitude of microplastics burden and their clinical consequences in at-risk populations have not been systematically characterized through a large-scale prospective cohort study.

To address these critical knowledge gaps, we established the Zhuhai Microplastics Exposure Cohort (Z-MEC) of patients with respiratory diseases, with the aim of systematically evaluating microplastic exposure, particularly the inhaled microplastics in bronchoalveolar lavage fluid (BALF), and linking them to the clinical outcomes. Beyond the identification and quantification of microplastics, the study protocol integrates detailed clinical phenotyping, including the assessment of inflammatory biomarkers, thyroid function, lipid profiles, etc. Furthermore, we collect multiple human biospecimens and plan to employ multi-omics approaches to explore the potential molecular mechanisms underlying the health impacts of microplastics exposure. The ongoing cohort Z-MEC is supposed to indicate potential health risk introduced by microplastics, and to provide important epidemiological evidences to inform risk assessment and regulatory strategies.

2. Method

2.1. Study Population and Design

Zhuhai is located in the southern part of China's Pearl River Delta region and is a coastal city with rapid urban development. Urbanizing coastal city has a dense transportation network and active human activities, and these factors may contribute

to environmental microplastics pollution and increase the exposure risks among residents. The Z-MEC study was conducted at the Fifth Affiliated Hospital of Sun Yat-sen University, a Grade A tertiary general hospital located in Zhuhai, Guangdong Province, China. Equipped with advanced medical technology and ample resources, this hospital treats a diverse and representative patient population. Patients recruited from this hospital for the study represent a broad spectrum of exposure sources and intensities to microplastics, thereby laying the groundwork for subsequent assessments of health effects. We recruited patients with respiratory diseases who consented to microplastics analysis. Those who underwent bronchoscopy as part of their routine clinical care were further subjected to bronchoalveolar lavage fluid (BALF) collection, with the aim of conducting a detailed assessment of airborne microplastics burden in the deep lung. Patients meeting the following criteria were enrolled in the study: 1) age 18 years or older; 2) no history of invasive lung surgery within the past half-year; 3) no infectious diseases like tuberculosis or viral hepatitis. Baseline recruitment for the Z-MEC study was initiated in October 2020 and finalized in November 2022. Through a two-year targeted enrolling period, a total of 700 patients were informed about and consented to participate in the study. The study protocol was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (approval number: 2018-K51-4).

The Z-MEC study is a hospital-based prospective cohort study, in which all the participants completed routine outpatient or admission examinations, an electronic structured questionnaire, and biospecimen collection at baseline (**Figure 1**). A trained investigator or physician would guide the patient through the above process. Detailed information about the patients' diagnosis, treatments, medication histories, functional tests, radiology reports, and laboratory test results, was obtained from the individual electronic medical records.

2.2. Questionnaire

Demographic, socioeconomic, and lifestyle information regarding the sex, age, marriage, income, residence, smoking and dietary habits, exercise status, and sleep pattern was recorded through an electronic questionnaire. Meanwhile, we also collected information on the potential exposure pathways and sources of microplastics, such as the distance between the property and major roads or coastlines, traffic exposure duration, home renovation situation, etc. In addition, we also investigated the subjects' occupational exposure history, medical history, allergy history, and family history. For lung cancer patients, the Lung Cancer Symptom Scale (LCSS) was conducted additionally [17]. For patients with chronic obstructive pulmonary disease (COPD), the COPD Assessment Test (CAT) was adopted to evaluate the impact of symptoms [18]. Strict quality control measures were implemented throughout the survey process, including standardized pre-survey training for field staff, daily verification of questionnaires by supervisors, and timely progress reports to ensure survey quality and timeliness. Following the export of electronic data, data cleaning and logical checks were performed by professional statisticians who were not involved in the study design.

2.3. Laboratory Examinations

The laboratory examinations a patient undergoes are determined by the clinician as needed during the normal course of medical care. Common tests include blood gas analysis, complete blood count, blood glucose, lipid profile, thyroid function, liver and kidney function, cancer serum markers, etc. All laboratory tests were conducted under standardized laboratory conditions and followed a unified quality control procedure. In addition to recording baseline laboratory data, changes in essential laboratory indices were also monitored during the scheduled follow-up visits.

2.4. Biospecimen Sampling

The scheduled biological specimens comprise BALF, fasting peripheral blood, and midstream random urine, with blank sampling controls set for each kind. For patients who were subjected to bronchoscopy during their normal treatment course, lower respiratory tracts were lavaged using a fiberoptic bronchoscope (P–290, Q–290, and 1TQ–290; Olympus, Tokyo, Japan) to collect their BALF samples. During bronchoalveolar lavage, approximately 20 mL of lavage fluid is instilled per cycle and immediately recovered via negative pressure suction, resulting in a total lavage volume of 120–300 mL. All the biospecimens collected were transferred into sterile glass containers, then aliquoted and stored at −80 °C for future analysis.

2.5. Microplastics Measurement

For pretreatment, to avoid microplastic contamination, all the necessary reagents were filtered using a stainless-steel membrane with a pore size of 0.45 μm (Youmi Industrial Co., Ltd., Shanghai, China). An excess of 68% nitric acid (Sinopharm Chemical Re-agent Co., Shanghai, China) was added to the BALF samples to digest the natural organic matters for 48 hours at a room temperature of 25 °C, followed by a three-hour heating at 60 °C. The subsequent filtration was conducted with a 13 μm stainless-steel membrane (Youmi Industrial Co., Ltd., Shanghai, China) under vacuum conditions (SHZ-D(III), Qiuzuo Technology Co., Ltd., Shanghai, China), as the detection range of the LDIR is 20–500 μm. The filtered membrane was then repeatedly washed with analytical grade ethanol (Titan Technology Co., Ltd., Shanghai, China) in an ultrasonic cleaner operating at 40 Hz, and the obtained eluate was subsequently concentrated to 100 μL by the infrared rapid desiccator. The concentrated solution was transferred to a high-reflectivity microscope slide (Agilent Technologies, Santa Clara, CA, USA) and allowed to evaporate naturally prior to microplastics analysis [19].

Inhaled microplastics in BALF were then qualitatively and quantitatively analyzed using a laser direct infrared (LDIR) spectrometer with a detection range of 20–500 μm (Model 8700, Agilent Technologies, USA). The LDIR system rapidly scans the entire microscope slide using infrared light of 1800 cm^{-1} via a quantum cascade laser. Once a suspicious particle is located, it is immediately subjected to full-spectrum analysis in the mid-infrared wavelength range (900–1800 cm^{-1}). By comparing spectra against a standard microplastic library (Agilent Technologies, USA) and a supplementary library, specific microplastic types were identified. A quality score was produced from spectral comparison, which was used to characterize the consistency between the spectral curves of detected substances and those of the

standard materials. The quality score ranges from 0 to 1, with higher values indicating a greater probability of the specific microplastic being present. Based on previous researches and to ensure the accuracy of microplastic detection, a relatively high threshold value of 0.75 was selected in this study [20–22]. The characteristics of microplastics include amount, composition, and shape parameters. We defined the abundance of microplastics as the amount of microplastic particles per gram (N/g) of BALF. By analyzing the composition, the specific types of microplastics and their proportions in BALF are obtained. Shape parameters were calculated by LDIR based on graphical algorithms, including diameter, perimeter, area, aspect ratio, eccentricity, circularity, and solidity.

We used reference materials, including polyethylene (PE), polyethylene terephthalate (PET), polystyrene (PS), polypropylene (PP), and polyvinyl chloride (PVC), to conduct recovery experiments to evaluate the detection capability of LDIR for mixed microplastics. The reference materials were first ground in a liquid nitrogen environment and then analyzed to determine their initial quantities. The ground materials were subsequently subjected to the same pretreatment and analysis to determine their quantities after pretreatment. Finally, the two sets of analytical results were compared to determine whether these materials were quantitatively recovered (**Figure S1** in the Supplementary materials). The results demonstrated a high recovery rate across diverse microplastic types, with a range from 90.00% to 97.78% (**Table S1** in the Supplementary materials), which is consistent with those of prior studies adopting the same technique [21,22]. To validate the presence and to identify the shape of microplastic particles, scanning electron microscopy (Thermo Fisher Scientific, Waltham, MA, USA) was further utilized to analyze the microplastics detected by LDIR.

2.6. Quality Control for Microplastic Detection

In this study, we implemented a series of strict quality control measures to prevent potential external microplastic contamination throughout the exposure evaluation process. Firstly, all of the biospecimen collected was stored in a glass container to prevent potential contamination during storage. Secondly, a systematic control was also incorporated during the BALF collection period. We performed the lavage using the same bronchoscope setup and collected the saline solution in a sterile metal bowl; this sample served as the blank control for the sampling system. Thirdly, all reagents required for pretreatment were pre-filtered using a 1 μm stainless steel membrane and transferred to clean glass containers. Finally, an instrumental blank control test was performed before formally commencing batch testing. The results of microplastic detection in blank controls utilizing LDIR indicate that the methodology employed in this study generates minimal exogenous contamination (**Table S2**).

2.7. Follow-up Plan and Study Endpoints

Follow-up appointments are scheduled by clinicians based on the patient's medical history and treatment status. During the follow-up, self-reported respiratory or chronic diseases, such as pneumonia, COPD, asthma, chronic bronchitis, hypertension, hyperlipidemia, diabetes, cardiovascular diseases, and cancers, were

repeatedly collected and verified through medical records. In addition, important laboratory indices are also measured at each follow-up visit to advance molecular epidemiological studies exploring the early health impacts of microplastics.

2.8. Statistical Analysis

A comprehensive descriptive analysis of the baseline characteristics of the Z-MEC study was conducted. For continuous variables, the mean and standard deviation or the median and the 25th and 75th percentiles are presented, depending on their distribution; for categorical variables, the frequency and percentage are reported. Spearman correlation coefficients were used to assess the correlations across the abundance of different microplastic types. A two-tailed $P < 0.05$ indicates a statistically significant difference. R software (version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria) was used to perform the statistical analysis involved in this study.

3. Results

3.1. Baseline Characteristics

The workflow and objectives of the Z-MEC study are illustrated in **Figure 1**. The Z-MEC study included a total of 700 patients at baseline, with 479 who completed BALF collection. The demographic characteristics, lifestyle factors, and clinical data are presented and compared between the BALF group and the non-BALF group in **Table 1**. Compared with the non-BALF group, showed a higher proportion of females (over half), younger age, more never-smokers, more participants who do cooking, and a significantly higher proportion of lung cancer (over two-thirds of the group), whereas the proportion of chronic bronchitis was lower (all $P < 0.05$). These differences in characteristics might arise from the presence of contraindications to bronchoscopy, such as severe ventilatory dysfunction among elderly patients.

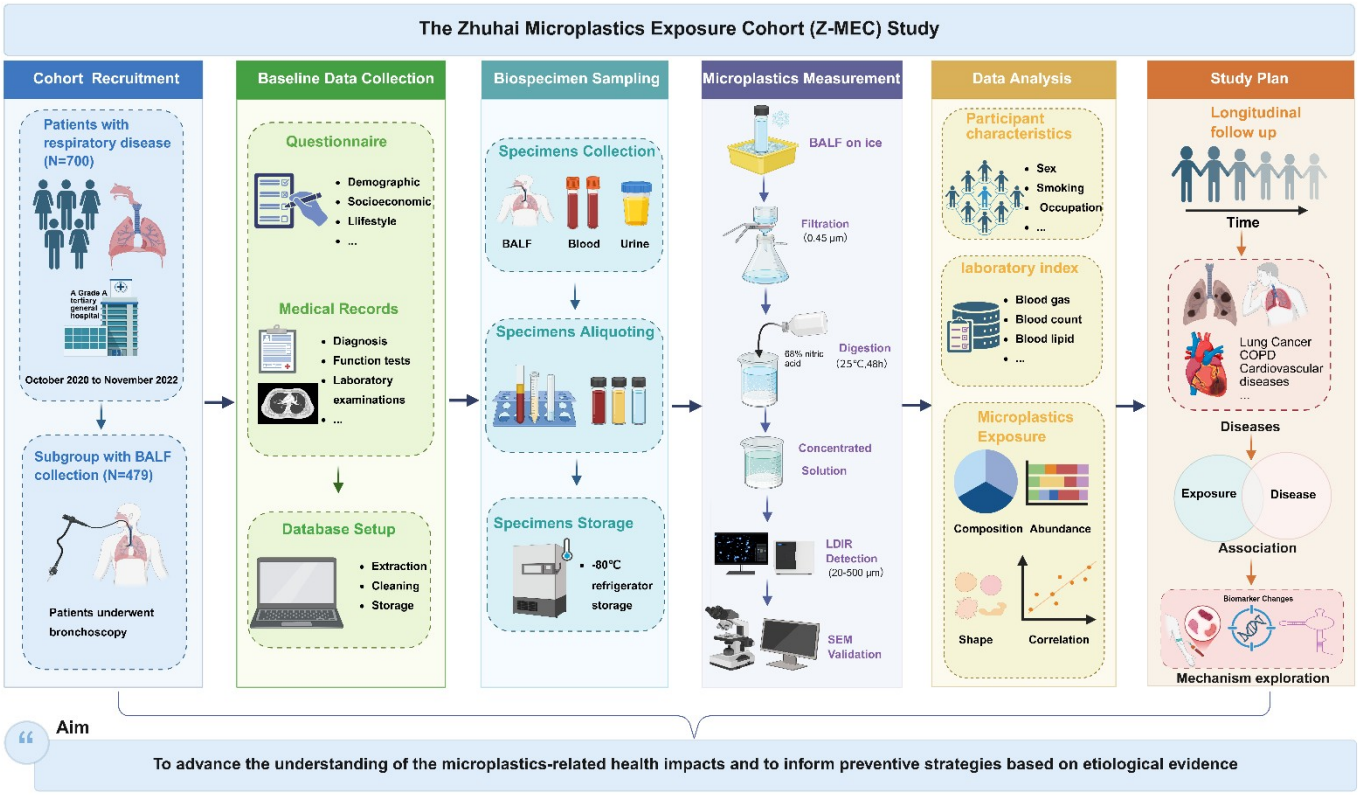

Figure 1. The workflow and objective of the Zhuhai Microplastics Exposure Cohort (Z-MEC) study.

Table 1. Basic characteristics of subjects in the Zhuhai Microplastics Exposure Cohort by BALF group.

Variables	BALF Group (N = 479)	Non-BALF Group (N = 221)	*P* Value
Sex, n (%)			0.045
Male	213 (44.47)	117 (52.94)	
Female	266 (55.53)	104 (47.06)	
Age, years (mean ± SD)	55.18 ± 12.23	57.55 ± 13.08	0.023
Height, cm (mean ± SD)	162.52 ± 7.74	162.40 ± 7.86	0.850
Weight, kg (mean ± SD)	61.16 ± 11.41	61.02 ± 13.06	0.893
BMI, kg/m^2 (mean ± SD)	23.12 ± 3.52	23.11 ± 4.86	0.980
Smoking status, n (%)			0.010
Current smoker	65 (13.57)	40 (18.10)	
Prior smoker	65 (13.57)	45 (20.36)	
Non-smoker	349 (72.86)	136 (61.54)	
Occupational exposure history, n (%)	87 (18.16)	29 (13.12)	0.119
Do cooking, n (%)	344 (71.82)	141 (63.80)	0.041
Daily traffic exposure time, n (%)			0.950
≤10 min	97 (20.25)	48 (21.72)	
11–30 min	161 (33.61)	66 (29.86)	
31–60 min	118 (24.63)	58 (26.24)	
61–120 min	58 (12.11)	26 (11.76)	
121–240 min	25 (5.22)	13 (5.88)	
>240 min	20 (4.18)	10 (4.52)	
Daily sedentary time, n (%)			0.944
≤1 hours	56 (11.69)	26 (11.76)	
1–3 hours	172 (35.91)	78 (35.29)	
3–5 hours	131 (27.35)	61 (27.60)	
5–8 hours	83 (17.33)	40 (18.10)	
8–12 hours	30 (6.26)	15 (6.79)	
>12 hours	7 (1.46)	1 (0.45)	
Clinical conditions, n (%)			
Lung cancer	338 (70.56)	92 (41.63)	<0.001
Hypertension	117 (24.43)	50 (22.62)	0.671
Hyperlipidemia	33 (6.89)	20 (9.05)	0.395
Diabetes	54 (11.27)	27 (12.22)	0.814
Chronic bronchitis	21 (4.38)	19 (8.60)	0.040
Asthma	13 (2.71)	5 (2.26)	0.925
COPD	7 (1.46)	3 (1.36)	1.000

Abbreviations: BALF, bronchoalveolar lavage fluid; BMI, body-mass index; COPD, chronic obstructive pulmonary disease.

As shown in **Table S3** in the Supplementary materials, patients underwent various baseline laboratory examinations based on their individual clinical needs. For complete blood gas analysis, the mean values of standard bicarbonate, whole blood lactate, and standard residual alkalinity were 24.19 ± 1.55 mmol/L, 1.67 ± 0.59 mmol/L, and −0.20 ± 1.95 mmol/L, respectively. The mean corrected blood pH was 7.40 ± 0.03, the mean corrected partial pressure of carbon dioxide (pCO_2) was 39.62 ± 3.56 mmHg, and the mean corrected oxygen partial pressure (pO_2) was 91.13 ± 16.58 mmHg. Of participants subjected to complete blood counts, the mean white blood cell count was 6.73 ± 3.26 ×10^9/L, with a mean neutrophil percentage of 59.91% ± 11.49% and a mean lymphocyte percentage of 29.41% ± 10.42%. In addition, the means of red blood cell count, hemoglobin, and hematocrit were 4.47 ± 0.64 ×10^{12}/L, 130.13 ± 17.22 g/L, and 39.39% ± 4.80%, respectively. The mean value was 88.86 ± 7.93 fL

for mean corpuscular volume (MCV), and 252.78 ± 73.23 ×10⁹/L for platelet count. For blood biochemical indicators, the mean levels of glucose, the Alanine aminotransferase (ALT)/Aspartate aminotransferase (AST) ratio, blood creatinine, and the estimated glomerular filtration rate (eGFR) were 5.93 ± 2.22 mmol/L, 1.37 ± 0.61, 70.57 ± 37.04 μmol/L, and 92.23 ± 18.32 mL/min/1.73 m², respectively. Regarding the blood lipid profile, the mean value was 1.25 ± 0.66 mmol/L for total triglyceride, 4.67 ± 1.08 mmol/L for total cholesterol, 1.34 ± 0.43 mmol/L for high–density lipoprotein (HDL), and 2.78 ± 0.90 mmol/L for low-density lipoprotein (LDL). Thyroid function indices were available for about 478 participants, among whom the mean thyroid-stimulating hormone (TSH) was 2.26 ± 3.96 μIU/mL, mean free thyroxine (FT4) was 16.41 ± 2.82 pmol/L, and mean free triiodothyronine (FT3) was 4.75 ± 0.80 pmol/L.

3.2. Evaluation of Inhaled Microplastics in BALF

The detection profile of microplastics in BALF is summarized in **Table 2** (representative LDIR and SEM images of microplastics were shown as **Figures S2–3)**. Microplastics were detected in the BALF of 461 subjects (96.24%), indicating a high detection rate of inhaled microplastics exposure in lower respiratory tract. The median abundance of total microplastics was 115.02 particles (N) per gram (g) of BALF, with an interquartile range (IQR) of 34.77–303.43 N/g. The top 10 identified microplastics were polyethylene (PE), high-density polyethylene (HDPE), polyurethane (PU), polyvinyl chloride (PVC), rubber, polytetrafluoroethylene (PTFE), polyethylene terephthalate (PET), polypropylene (PP), acrylates (ACR), and polystyrene (PS), with a detection rate of 67.04%, 51.57%, 49.48%, 43.42%, 35.91%, 35.28%, 34.03%, 32.99%, 24.01%, 22.55%, respectively. The median abundance of PE, the most commonly detected microplastic type, was 9.40 N/g (IQR, 0.00–58.35 N/g) of BALF, followed by HDPE with 4.75 N/g (IQR, 0.00–28.02 N/g). The median abundance for all other types of microplastics was 0, indicating a relatively low concentration.

Table 2. Detection profile of top 10 microplastics in BALF (N = 479).

Microplastic Type	Detectable Case (%)	Abundance (N/g of BALF)*		
		Q25	Q50	Q75
Total MPs	461 (96.24)	34.77	115.02	303.43
PE	321 (67.01)	0.00	9.40	58.35
HDPE	247 (51.57)	0.00	4.75	28.02
PU	237 (49.48)	0.00	0.00	9.80
PVC	208 (43.42)	0.00	0.00	9.95
Rubber	172 (35.91)	0.00	0.00	13.97
PTFE	169 (35.28)	0.00	0.00	4.93
PET	163 (34.03)	0.00	0.00	4.85
PP	158 (32.99)	0.00	0.00	4.87
ACR	115 (24.01)	0.00	0.00	0.00
PS	108 (22.55)	0.00	0.00	0.00

Abbreviations: ACR, Acrylates; BALF, Bronchoalveolar lavage fluid; HDPE, High-density polyethylene; MPs, microplastics; PE, Polyethylene; PET, Polyethylene terephthalate; PS, Polystyrene; PTFE, Polytetrafluoroethylene; PP: polypropylene; PU, Polyurethane; PVC, Polyvinyl chloride. * The abundance of microplastics in BALF was presented as particles (N) per gram (g) of BALF. Due to the skewed distribution, quantile values are exhibited.

The correlation analysis of the abundance across different microplastic types were shown in **Figure 2**. Overall, positive correlations between different types of microplastics are relatively prevalent, yet the majority of microplastic types fail to exhibit statistically significant correlations. Notably, the total microplastics abundance showed significant and relatively strong positive correlations with several microplastic types, including PE (r = 0.94), rubber (r = 0.75), and PP (r = 0.69). Additionally, a moderate correlation was also observed among PE, PP, rubber, PU, and ACR, with a correlational coefficient of 0.60 for PE and rubber, 0.56 for PE and PP, 0.56 for PP and rubber, and 0.35 for PU and ACR (all P <0.05).

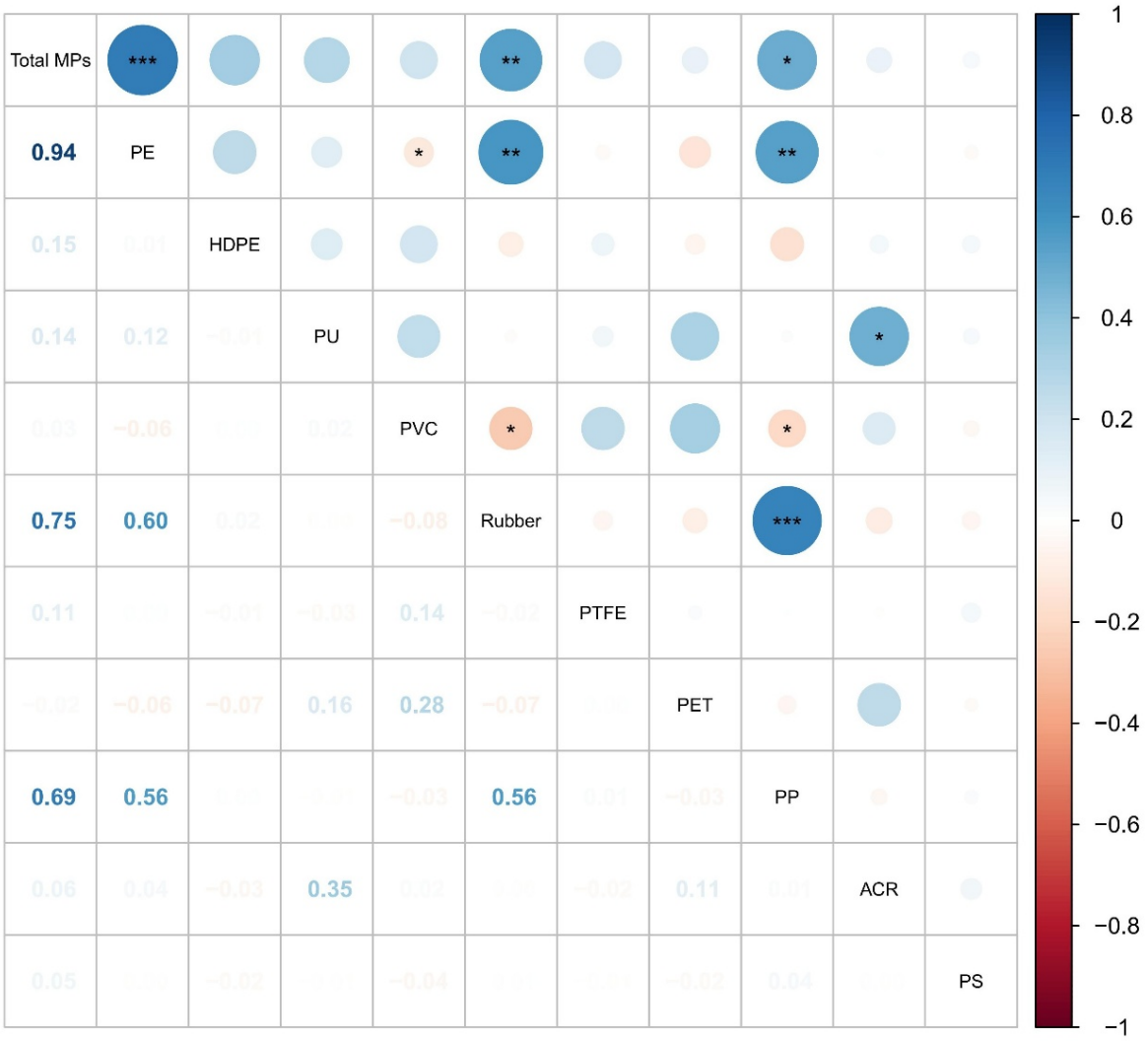

Figure 2. Correlations of Microplastics abundance in detectable subjects. Abbreviations: ACR, Acrylates; HDPE, High-density polyethylene; MPs, microplastics; PE, Polyethylene; PET, Polyethylene terephthalate; PS, Polystyrene; PTFE, Polytetrafluoroethylene; PP: polypropylene; PU, Polyurethane; PVC, Polyvinyl chloride. Shown is the Spearman's correlation coefficient across the abundance of top 10 detectable microplastic types in bronchoalveolar lavage fluid. Larger circular areas in the upper right panel indicate higher correlation coefficients, with blue tones representing positive correlations and orange tones indicating negative correlations. Significance symbols are marked at the center of each circle, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

The distribution and differences in the shape parameters of microplastics were illustrated in **Figure 3**. Regarding particle size, the median diameter of total microplastics was 36.78 μm (IQR, 31.92–46.35 μm). Compared to total microplastics, PS, HDPE, PE, and PET exhibited larger median diameters of 45.04 μm (30.01–64.91 μm), 43.88 μm (34.88–57.54 μm), 40.68 μm (32.77–54.55 μm), and 37.00 μm (30.38–59.02 μm), respectively. In contrast, the median diameters of PTFE and PVC were similar to that of total microplastics, at 36.56 μm (29.32–48.70 μm) and 36.78 μm (28.42–48.29 μm), respectively. Polymers with relatively smaller diameters included ACR, PU, PP, and rubber, with rubber having the smallest diameter at 28.07 μm (23.93–39.31 μm). In terms of aspect ratio, the median value for total microplastics was 1.27 (1.19–1.50). Except for HDPE (1.13[1.08–1.24]) and PE (1.27[1.14–1.50]), the median aspect ratios of all other types were higher than that of total microplastics, including ACR (1.64[1.25–2.34]), PET (1.63[1.26–2.24]), PS (1.57[1.25–1.87]), PVC (1.55[1.21–2.29]), PTFE (1.46[1.23–2.04]), PP (1.46[1.25–1.76]), PU (1.44[1.25–2.00]), and rubber (1.33[1.22–1.57]). The median perimeter for total microplastics was 144.25 μm (120.96–185.71 μm); PS, PE, PET, ACR, HDPE, and PTFE were generally larger perimeters, while PP, PVC, PU, and rubber were smaller. In terms of area, the median area of total microplastics was 1062.50 μm² (800.00–1687.50 μm²). The area distribution of PS, HDPE, PE, PET, and PTFE was generally higher than that of total microplastics, while the areas of PVC, ACR, PU, PP, and rubber were relatively smaller. In the case of eccentricity, only PVC (0.75 [0.70–0.84]) exhibited a markedly higher eccentricity than that of total microplastics (0.71 [0.67–0.74]); while PP (0.68 [0.63–0.73]) and rubber (0.64 [0.59–0.69]) showed an obviously lower eccentricity. As for circularity and solidity, the median value was 0.78 (IQR, 0.65–0.84) for circularity and 0.94 (0.90–0.96) for the solidity of total microplastics. In comparison to those of total microplastics, HDPE and PE, rather than other types, exhibited higher values both in circularity and solidity.

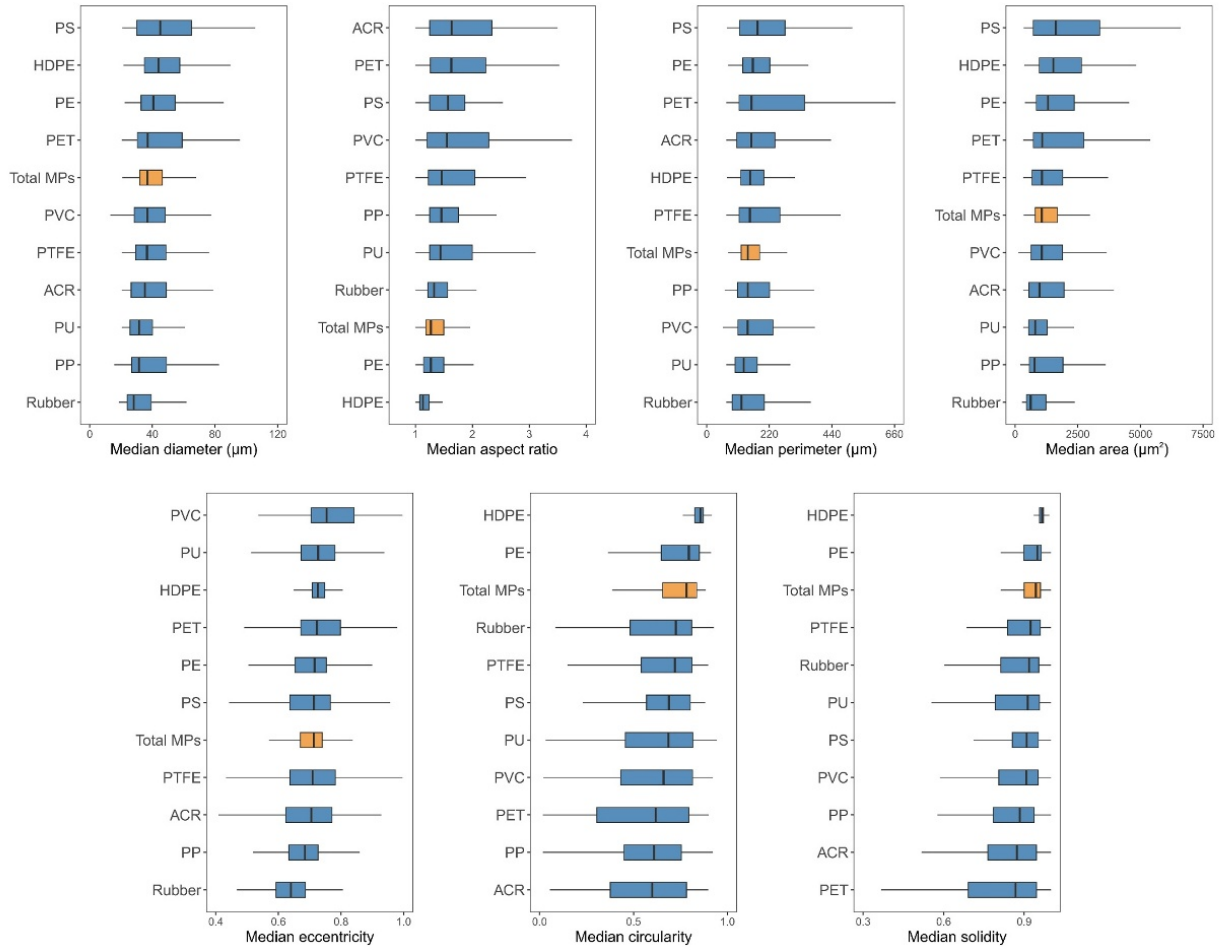

Figure 3. Distributions of shape parameters of microplastics in BALF. Abbreviations: ACR, Acrylates; HDPE, High-density polyethylene; MPs, microplastics; PE, Polyethylene; PET, Polyethylene terephthalate; PS, Polystyrene; PTFE, Polytetrafluoroethylene; PP: polypropylene; PU, Polyurethane; PVC, Polyvinyl chloride. Shape parameters of each microplastic, including diameter, aspect ratio, perimeter, area, eccentricity, circularity, and solidity, were detected by the laser direct infrared system. The box plots were used to illustrate the distribution of median value of each shape characteristic for total microplastics (orange-filled box) and the top 10 detected microplastic types (blue-filled boxes).

4. Discussion

The Zhuhai Microplastics Exposure Cohort study provides a pioneering large-scale prospective patient-based cohort platform for investigating the health effects of microplastics. This study systematically analyzed the baseline characteristics of inhaled microplastic burden in BALF from 479 patients with respiratory diseases and collected comprehensive biomonitoring data, promising to serve as a robust foundation for etiological research on the health risks associated with microplastics.

Baseline exposure data from the Z-MEC study revealed that 96.24% of participants had microplastics identified in their BALF, indicating the widespread presence of inhaled microplastics in the lower respiratory tracts. While the laboratory testing results indicate that the majority of the parameters measured in the participants fell within the normal reference range [23,24]. Prior studies involving smaller sample sizes have also frequently detected the presence of microplastics in specimens such as lung tissue, sputum, or BALF [11,25,26]. However, earlier studies have typically

employed traditional methods such as μ-Raman spectroscopy or Fourier transform infrared (FTIR) [11,27], which feature fundamentally different detection mechanisms from the novel LDIR method used in this study, making it challenging to directly compare differences in microplastic burden. The detection method adopted in this study offers significant advantages: reliable quantification data are obtained through rigorous Q/C procedures (i.e., the setup of sampling and testing controls and the utility of glassware for storage) and intuitive spectral comparisons via LDIR, with validation by SEM, thereby facilitating the precise detection of microplastic exposure; additionally, detailed morphological data were collected for individual microplastic particles, significantly enriching the multidimensional assessment of microplastic exposure burden and potentially advancing strategies for evaluating the health risks associated with microplastics. Based on the comprehensive characterization of inhaled microplastics from the study population, and by integrating laboratory examinations with disease surveillance, the Z-MEC study will support a rigorous evaluation of the microplastics–health relationship.

Consistent with previous studies, our findings indicate that microplastics such as PE, HDPE, PU, PVC, rubber and PTFE are the primary types inhaled via the respiratory route [9,26]. The sources of airborne microplastics are closely related to specific human activities and exhibit pronounced spatial heterogeneity. PU and PE are significantly enriched in indoor environments, due to the accumulation of microfragments from soft furnishings and packaging materials under poor ventilation conditions [28,29]. In contrast, the composition of microplastics in inland outdoor areas (particularly around transportation hubs) is dominated by local traffic load and construction activities, resulting in the notable enrichment of rubber and PVC [30]. Notably, lightweight polymers such as PE and HDPE are frequently re-emitted into the atmosphere from the ocean surface via wave-generated aerosol droplets, leading to higher concentrations in coastal regions than in inland rural areas [31]. Additionally, PTFE displays a point-source distribution pattern, occurring mainly in highly industrialized regions or industrial textile processing zones [28]. Moreover, this study found a certain degree of correlation between different types of microplastics, suggesting that these polymers may originate from similar environmental exposure pathways. For instance, PE and HDPE, which are widely used in packaging materials and plastic products, often co-occur in the samples, reflecting a common pollution source [32]. Therefore, the public should make a conscious effort to minimize these potential exposures, and relevant authorities are urged to consider implementing measures to protect public health.

Existing studies on the toxic effects of microplastics have largely focused on dose-response relationships, while overlooking the potential impact of the shape characteristics of microplastics in real-world environments [28]. Through LDIR analysis, we have mapped out a landscape of the morphological characteristics of microplastics in BALF. This study provides direct evidence that the actual inhaled microplastics are predominantly irregular in shape, which may be associated with the long-term degradation and mechanical fragmentation of plastic materials in the environment. It is worth noting that, despite variations in the distribution of shape parameters among different microplastic types, the overall trend is similar. Previous studies have shown that smaller and irregularly shaped microplastics are more likely

to be deposited in the deeper regions of the respiratory system, particularly in the alveolar regions, where they may remain for extended periods [33,34]. Therefore, the particle size and morphological characteristics of microplastics may play an important role in their biological deposition and potential toxicity. It is noteworthy that our findings show the median diameter of total microplastics in BALF reached 36.77 μm, which is larger than the size generally considered to be that of inhalable particles (those with an aerodynamic diameter of less than 10 μm). Such a paradox may originate from the elongated shape of microplastics (like filamentous appearance) or potential aggregation effects [35,36]. Nevertheless, these findings emphasize the urgent need for more research into the toxic effects of irregularly shaped microplastics, as such microplastics are highly prevalent in real-world scenarios, yet our understanding regarding them remains extremely limited.

This study has some limitations. Firstly, the Z-MEC study has not yet completed its follow-up. Only cross-sectional analyses are currently available to explore the association between microplastic exposure and health outcomes, which are insufficient to support causal inferences. Secondly, the study participants were derived from a clinical population, the majority of whom were lung cancer patients, thereby limiting the extrapolation. Finally, this study is currently a single-center study conducted at a single hospital, which restricts the expansion of the cohort and poses challenges in ensuring a high follow-up rate. Therefore, the Z-MEC study will be dedicated to developing a large-scale, multicenter cohort with long-term follow-up, with the aim of providing crucial epidemiological evidence for the risk assessment of microplastics.

5. Conclusion

Collectively, the establishment of Z-MEC provides an important platform for investigating the health effects of microplastics. The baseline examinations confirm that microplastics are widely present in respiratory tracts and exhibit diverse polymer types and irregular shape characteristics. Further research will integrate cross-sectional and longitudinal study designs to investigate the association between microplastic exposure and health outcomes. Additionally, molecular epidemiological studies based on laboratory analyses and multi-omics data will be conducted to explore underlying biological mechanisms. These efforts are expected to advance understanding of the health risks associated with microplastics and inform prevention and intervention strategies based on etiological evidence.

Supplementary Materials: Figure S1: Flow diagram of Recovery Test; Figure S2: Representative microplastics characterized by laser direct infrared; Figure S3: Representative scanning electron microscopy; Table S1: Recovery rates of mixed microplastics detected by laser direct infrared; Table S2: Abundance of microplastics in blank controls; Table S3: Laboratory testing results of participants in the Zhuhai Microplastics Exposure Cohort.

Author contributions: Y.Z. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, Y.Z., L.F. and S.W. (Shaojuan Wang); Methodology, L.F., C.Z.

and L.Q. (Lan Qiu); Software, W.L., M.L. and H.S.; Validation, Y.Z., L.F., and X.L.; Formal Analysis, L.F., S.W. (Shaojuan Wang), C.T. and M.L.; Investigation, X.X., Y.C., Z.D. and L.Q. (Liqiu Qiu); Resources, Y.Z. and J.L.; Data Curation, L.F., S.W. (Shaojuan Wang) and C.Z.; Writing – Original Draft Preparation, L.F and S.W. (Shaojuan Wang); Writing—Review & Editing, Y.Z. and L.F.; Administrative, technical, or material support, S.W. (Shuguang Wang), L.Q (Lan Qiu). and M.H.; Visualization, J.F., J.W. and C.T.; Supervision, Y.Z., L.J. and X.L.; Project Administration, Y.Z., L.J. and X.L.; Funding Acquisition, L.F. All authors read and approved the final manuscript.

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