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ORIGINAL RESEARCH

Significance of *Stenotrophomonas maltophilia* When Detected in Sputum of Ambulatory Patients with COPD

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Introduction: *Stenotrophomonas maltophilia* is an emerging Gram-negative MDR bacteria. In patients with chronic obstructive pulmonary disease (COPD), it is mostly found in those with severe exacerbation of COPD requiring mechanical ventilation. The significance of *S. maltophilia* when detected in the sputum of ambulatory patients with COPD is uncertain.

Objective: To access the prevalence and the risk factors of the presence of *S. maltophilia* in the sputum of ambulatory patients with COPD and to determine whether it was associated with prognosis.

Methods: All consecutive unselected ambulatory patients with GOLD 2–4 COPD were recruited between January 2017 and September 2019 from the COPD clinic of a tertiary care hospital. Presence of *S. maltophilia* was defined by a positive sputum culture for *S. maltophilia*. Demographics, COPD characteristics, comorbidities and known predisposing risk factors associated with *S. maltophilia* were collected from medical records.

Results: *S. maltophilia* was detected in the sputum of 41/393 (10%) of study participants. Comorbidities, exacerbation, use of oral steroids and carbapenems in the previous year were risk factors for the presence of *S. maltophilia*. After adjusting on confounding factors associated with mortality including age, Charlson comorbidity index and FEV_1, *S. maltophilia* was significantly associated with mortality (adjusted hazard ratio 2.3; 95% CI 1.1–4.9).

Conclusion: In the current study, we found that 10% of ambulatory patients with GOLD 2–4 COPD had *S. maltophilia* detected in their sputum. In addition, *S. maltophilia* may represent a marker of overall morbidity in patients with COPD.

Keywords: *Stenotrophomonas maltophilia*, pulmonary disease, chronic obstructive, risk factors, prognosis

Introduction

Bacterial colonization occurs in 30% of patients with chronic obstructive pulmonary disease (COPD) when in a stable phase and it contributes to disease progression and recurrence of acute exacerbation of COPD (AECOPD).[1] *Stenotrophomonas maltophilia* is an emerging Gram-negative MDR bacteria that is most commonly associated with respiratory infections in humans.[2] In patients with COPD, it is mostly found in those with severe AECOPD requiring mechanical ventilation and associated with worse survival.[3] The significance of *S. maltophilia* when detected in the sputum of ambulatory patients with COPD is uncertain. Therefore, we aimed at investigating the prevalence and the risk factors of the presence of *S. maltophilia* in

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the sputum of ambulatory patients with COPD and to determine whether it was associated with prognosis.

Methods

This retrospective study involved all consecutive unselected ambulatory patients with GOLD 2–4 COPD recruited between January 2017 to September 2019 from the COPD clinic of a tertiary care hospital (Institut universitaire de cardiologie et de pneumologie de Québec). The study was approved by the local Research Ethics Board (CRIUCPQ, 2020–3317). Data were fully anonymized in a standardized case report form to ensure data confidentiality. As such, written consent from the patients or their guardians was exempted and this study was carried out in full compliance with the Helsinki Declaration.

Presence of *S. maltophilia* was defined by a positive sputum culture for *S. maltophilia*. Sputum specimens were plated and cultured on usual agar media. Colonies fitting S. maltophilia phenotypic characteristic were then isolated. Identification and antibiotic susceptibility were performed with the Vitek 2 Compact System (Biomerieux, Canada). In case of inconclusive results, colonies were identified using either Vitek MS or Bruker's MALDI/TOF mass spectrometry (Bruker, Canada).

Demographics, COPD characteristics, comorbidities and known predisposing risk factors associated with *S. maltophilia* were collected from medical records. We searched for potential host factors potentially associated with the detection of *S. maltophilia* using bivariate correlations that were further summarized using focused principal component analysis (FPCA, "psy" package within the R environment) as previously described.[4] A multivariate logistic regression model with backward stepwise selection was then performed to confirm which host factors, amongst those that were identified with the FPCA, were significantly associated with the presence of *S. maltophilia* in the sputum. Finally, the impact of *S. maltophilia* sputum detection on all-cause mortality was evaluated using Kaplan-Meier survival analysis, Log rank test, and Cox regression. Statistical analysis was performed with R version 4.0.3 and RStudio version 1.4.1103 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Three-hundred ninety-three patients with GOLD 2–4 COPD were included in the study. Mean age was 69.0 ± 8.5 years and 57% were male. Mean FEV_1 was 44.3 ± 16.5% of the predicted value and 49% had GOLD D COPD (Table 1). 82% were taking triple inhaled therapy, 23% were on prophylactic azithromycin and 6% had long-term oral steroids (defined by a prednisone equivalent dose of >7.5 $mg \cdot day^{-1}$ for more than 3 months). The most frequent comorbidities were hypertension (52%), diabetes (17%), coronary artery disease (CAD) (11%) and cancer in the previous five years (15%). No patient was admitted to the ICU department in the 12-month period prior to data collection.

S. maltophilia was detected in the sputum of 41/393 (10%) of study participants and *Pseudomonas aeruginosa* was found in 55/393 patients (14%); in 12/41 patients, *S. maltophilia* was identified during the course of a moderate AECOPD. No difference was found between patients in which *S. maltophilia* was detected in stable condition and during an exacerbation. In six patients, *S. maltophilia* persisted in sputum for more than one year in sputum. Susceptibility of *S. maltophilia* strains was of 98% for levofloxacin, 98% for minocycline, 85% for trimethoprim/sulfamethoxazole and 46% for ceftazidime.

From the available clinical data, based on the FPCA, two categories of host factors were significantly associated with the presence of *S. maltophilia* in the sputum (Figure 1). The first category was directly related to COPD and included the occurrence of moderate and/or severe exacerbations in the 12-month prior to data collection (yes or no), use of antibiotics (especially carbapenems), long-term oral steroids, inhaled corticosteroids, azithromycin and CAT score. The second category was related to comorbidities and included hypertension, cancer, cerebrovascular disease, CAD and chronic heart failure (CHF).

The following host factors were independently associated with *S. maltophilia* sputum detection in the multivariate analysis: CAD and/or CHF (OR 2.7; 95% CI 1.3–5.7), cancer in the previous 5 years (OR 3.2; 95% CI 1.4–7.2), long term use of oral steroids (OR 4.2; 95% CI 1.3–12.5), the occurrence of moderate and/or severe AECOPD (OR 5.7; 95% CI 1.9–24.7) and carbapenem use (OR 13.5; 95% CI 4.9–39.2) in the 12-month period prior to the data collection.

Mean follow up was 25.9 ± 11.2 months and 25.4 ± 10.6 months in patients with and without *S. maltophilia* in the sputum, respectively. During the follow-up period, 34 patients died, of these 9/41 (22%) had *S. maltophilia* detected in their sputum and 25/352 (7%) had not. The

Table 1 Main Characteristics of Patients with COPD Included in the Study

	Presence of *S. maltophilia*	Controls	p-value
	n = 41	n = 352	
Demographics			
Age, year s	71.0 ± 8.2	68.9 ± 8.5	0.12
Male	28 (68)	195 (55)	0.11
Body mass index, kg/m2	27.2 ± 5.6	27.2 ± 6.3	0.99
Current smokers, %	8 (20)	84 (24)	0.53
Cumulative smoking exposure, pack-years	42.8 ± 18.5	41.3 ± 19.4	0.64
Disease severity			
CAT score	24.0 ± 7.8	20.9 ± 7.4	**0.01**
AECOPD in the previous year	38 (93)	228 (65)	**< 0.0001**
Moderate exacerbations	2.5 ± 1.9	1.4 ± 1.6	**< 0.0001**
Severe exacerbations	0.9 ± 1.4	0.1 ± 0.4	**< 0.0001**
Number of hospital admission in the previous year	1.1 ± 1.7	0.2 ± 0.6	**< 0.0001**
GOLD A/B/C/D	0/8/1/32	17/161/12/162	**0.001**
Lung function			
FEV1 post BD, L	0.98 ± 0.35	1.13 ± 0.48	0.06
FEV1 post BD, % predicted	39.3 ± 14.6	44.9 ± 16.7	0.10
GOLD stage 1/2/3/4	0/10/20/11	8/118/160/66	0.44
Therapy			
LAMA	40 (98)	340 (97)	1.00
LABA	39 (95)	342 (97)	0.36
ICS	40 (98)	295 (84)	**0.02**
Triple therapy	38 (93)	284 (81)	0.08
Long term oral steroids	7 (17)	16 (5)	**0.001**
Macrolides	17 (42)	74 (21)	**0.003**
Antibiotics in the previous year	38 (95)	221 (63)	**< 0.0001**
Comorbidities			
Charlson comorbidity index	6.1 ± 2.7	4.6 ± 2.1	**< 0.0001**
CAD and/or CHF	21 (51)	100 (28)	**0.003**
Hypertension	28 (68)	177 (50)	**0.03**
Diabetes	9 (22)	58 (17)	0.38
Cerebrovascular disease	7 (17)	19 (5)	**0.004**
Cancer in the last 5 years	13 (32)	47 (13)	**0.002**
Chronic kidney disease	1 (2.5)	4 (1.1)	0.53
Bronchiectasis	8 (20)	34 (10)	0.06

Note: Values in bold are significant ($p < 0.05$).

Abbreviations: BD, bronchodilator; CAD, coronary artery disease; CAT, COPD assessment test; CHF, chronic heart failure; ECOPD, exacerbation of COPD; FEV1, forced expiratory volume in the first second; GOLD, global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroids; LABA, long-acting b2-agonist; LAMA, long-acting muscarinic antagonist.

Kaplan–Meier survival curve indicated that *S. maltophilia* sputum detection was significantly associated with mortality in this population (Log rank test p = 0.003). This association remained after adjusting on confounding factors associated with mortality including age, Charlson comorbidity index and FEV_1 (adjusted hazard ratio 2.3; 95% CI 1.1–4.9) (Figure 2).

Discussion

Studies regarding *S. maltophilia* in COPD are scarce and most were conducted more than 15 years ago. In these studies, prevalence of *S. maltophilia* ranged between 0.5% in stable COPD patients and 3% in those with severe AECOPD admitted to ICU.[1,3] However, prevalence and awareness of *S. maltophilia* have increased in the last

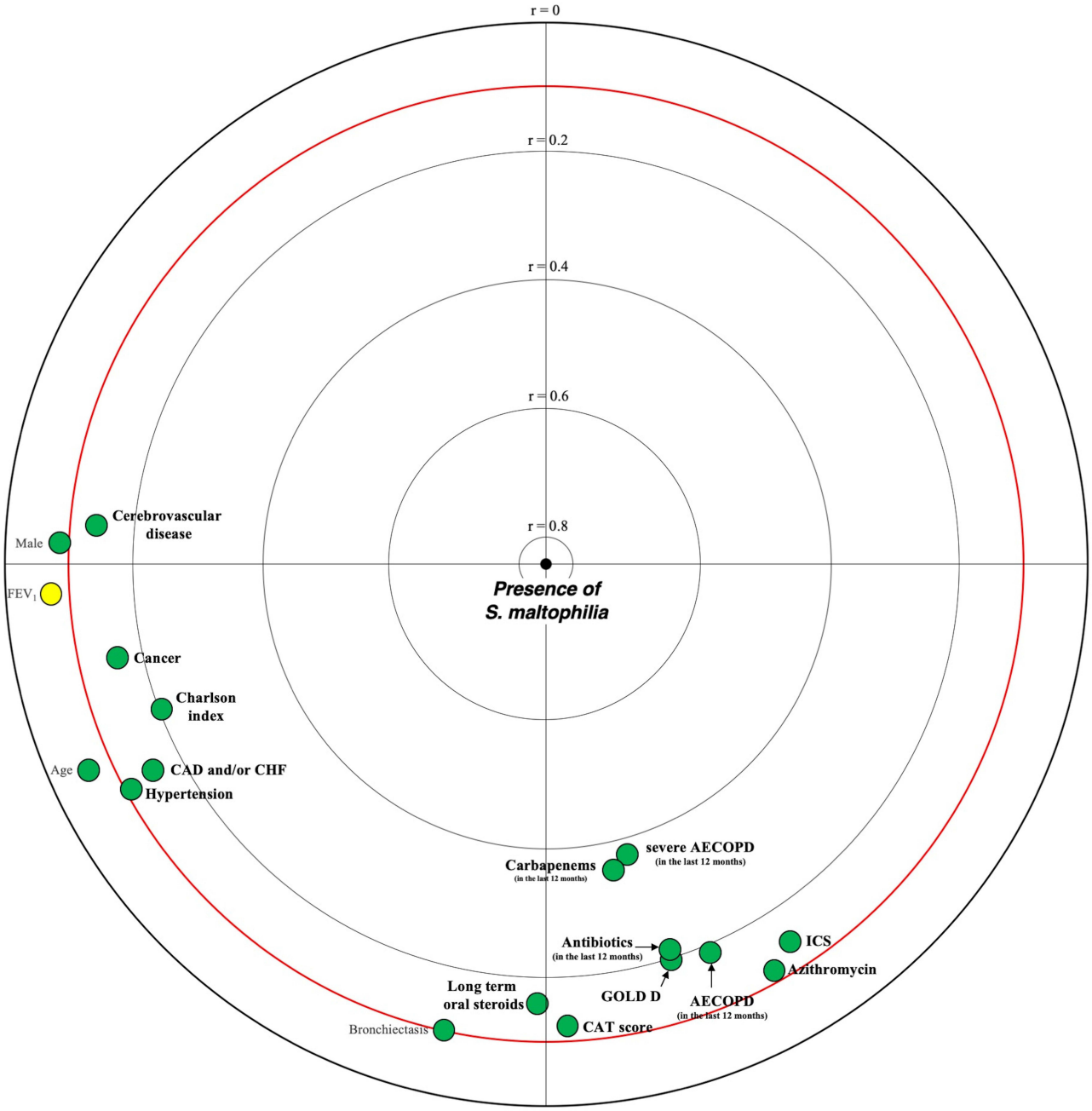

Figure 1 Focused principal component analysis (FPCA) for the association between presence of *S. maltophilia* and several host factors. FPCA is a simple graphical display of correlation structures focusing on a particular dependent variable. The display reflects primarily the correlations between the dependent variable and all other variables (covariates) and secondarily, the correlations among the covariates. The dependent variable (the presence of *S. maltophilia* in the sputum) is at the center of the diagram, and the distance from this point to a covariate faithfully represents their pairwise Spearman correlation coefficient (using ranked values of continuous variables). Green covariates are positively correlated and yellow covariates negatively correlated with the dependent variable. Covariates (in bold) inside the red circle are significantly correlated with the dependent variable (with a p value < 0.05). The diagram also shows relationships between covariates as follows: correlated covariates are close (for positive correlations, allowing identification of clusters) or diametrically opposite vis-a-vis the origin (for negative correlations), whereas independent covariates make a right angle with the origin.

decade and this bacteria now accounts for 1.4% of pathogens isolated from general population in Canadian hospitals.[5] Furthermore, refinement in microbiological techniques, including the use of selective culture media and of MALDI–TOF mass spectrometry have improved the ability to identify and isolate of *S. maltophilia* from polymicrobial cultures.[6,7] In the current study, we found a 10% prevalence of *S. maltophilia* isolation in ambulatory patients with COPD which is somewhat similar to that found in cystic fibrosis (14%).[8]

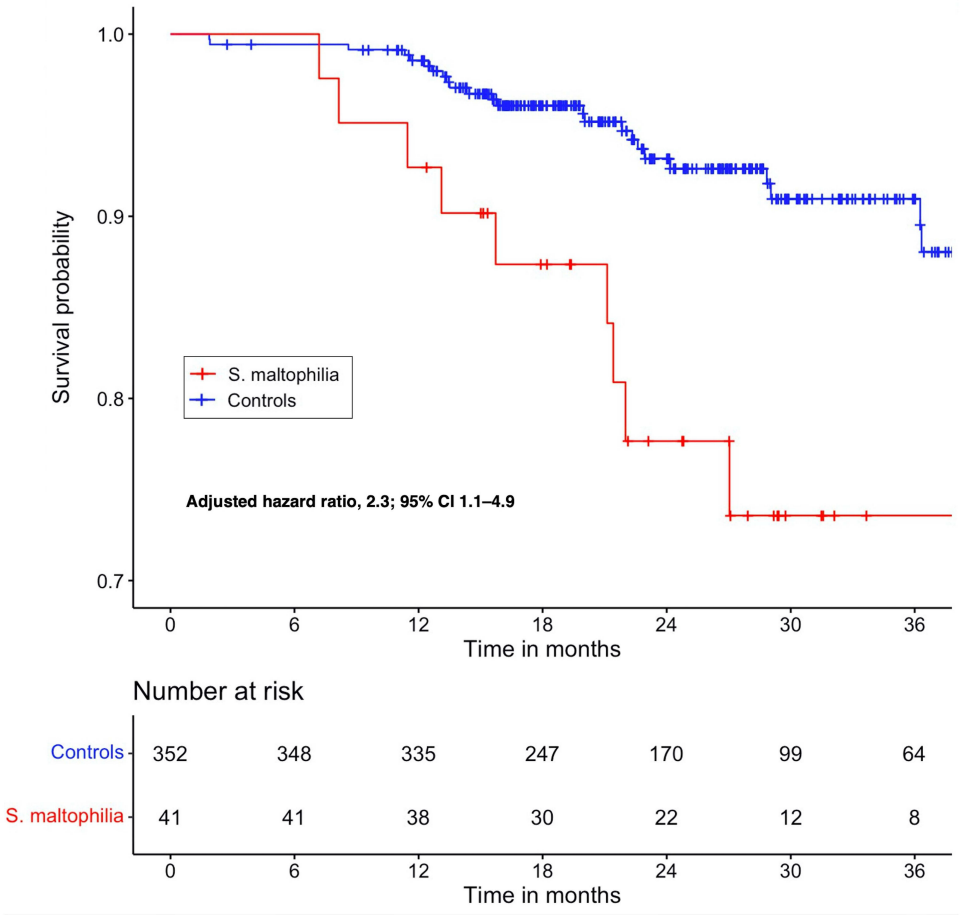

Figure 2 Kaplan–Meier survival curves over the first 36 months following sputum detection of *S. maltophilia*. Survival data was censored at 36 months. Mortality was adjusted for age, Charlson comorbidity index and FEV_1.

Risk factors for *S. maltophilia* sputum detection in the current study were similar to those found in cancer patients, immunocompromised hosts and individuals previously exposed to wide-spectrum antibiotics.[2,9,10] In addition, we found an association between *S. maltophilia* and COPD exacerbation, use of oral steroids and carbapenems which might represent targets for further preventive strategies.

As *S. maltophilia* may persist in the sputum of these patients for a long period of time, it may be difficult to ascertain the clinical significance of a positive culture result from the microbiology laboratory.[11] The present data suggest that in ambulatory patients with COPD, *S. maltophilia* may represent a marker of overall morbidity and its clinical significance should not be overlooked by clinicians. We found that the presence of *S. maltophilia* in the sputum was associated with increased mortality even after adjustment for potential confounders such as age, Charlson comorbidity index and FEV_1.

In conclusion, we found that: 1) 10% of ambulatory patients with GOLD 2–4 COPD had *S. maltophilia* detected in their sputum, 2) comorbidities, exacerbation, use of oral steroids and carbapenems were risk factors for the presence of *S. maltophilia* in the sputum, and 3) the latter may represent a marker of overall morbidity and a predictor of mortality in patients with COPD. Additional research is needed to determine the role of *S. maltophilia* in COPD.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or

critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Dr. Godbout reports grants and personal fees from AstraZeneca, Sanofi, Novartis and GSK, personal fees from Merck, Covis and TEVA, outside the submitted work. Dr. Maltais reports grants from GlaxoSmithKline, AstraZeneca, Sanofi, Novartis, Boehringer Ingelheim and Grifols, personal fees from GlaxoSmithKline, Boehringer Ingelheim, Grifols, Novartis, outside the submitted work. He also reports financial participation in Oxynov, a company which is developing an oxygen delivery system. The other authors have no conflicts of interest in this work.

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