PRTN3/FCER1A Transcriptomic Ratio Predicts Hospitalization in Primary Care Attenders With Respiratory Infection

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Abstract

Early detection of patients with respiratory infection at risk of deteriorating could help to improve their outcome by facilitating immediate transfer to the hospital to receive the adequate level of care. In this regard, gene expression profiling is emerging as a promising tool to identify patients with infection at risk of suffering a complicated outcome. In a cohort of patients with respiratory infection attending to an Emergency Room at a community health centre, we quantified expression levels in blood of five genes involved in the granulocyte biology that have been previously described to be linked to infection severity: MMP8 (matrix metalloproteinase 8), LCN2 (lipocalin-2), LTF (lactotransferrin) and PRTN3 (proteinase 3) and FCER1A (receptor for Fc fragment of IgE, high affinity I). Expression levels of these genes were evaluated to predict hospitalization. Multivariate analysis adjusted by the National Early Warning Score (NEWS), neurovascular disease, hypertension and age revealed that all these genes independently predicted hospitalization. Nonetheless, the ratio between PRTN3/FCER1A outperformed individual genes to predict necessity of hospitalization (OR [CI95%], p : 8.36 [2.02-34.52], 0.003). In conclusion, quantification of PRTN3/FCER1A gene expression ratio could represent a useful test to early identify those patients with respiratory infection at risk of deterioration in extra-hospital settings.

Introduction

Respiratory infection is one of the major causes of morbimortality worldwide (1) (2). Early detection of patients at risk of deteriorating could help to improve their outcome by facilitating immediate transfer to the hospital to receive the adequate level of care. In this regard, gene expression profiling is emerging as a promising tool to guide clinical decisions in respiratory (3) (4) and other kind of severe infections such as sepsis (5). Expression levels of genes involved in the granulocyte biology has been described to be altered in severe respiratory infections of viral (6) (7) or bacterial origin (8), responding to a phenomenon called “emergency granulopoiesis” (9). In consequence, granulocyte-related genes are potentially useful to detect patients with respiratory infections at risk of developing a complicated outcome. Nonetheless, current studies profiling gene expression in respiratory infections have been developed late in the course of the disease, once the patient is already hospitalised.

In the present study, we quantified the expression levels in blood of five of these granulocyte genes early after the onset of a respiratory infection, in attenders to an Emergency Room sited at a community health centre. Expression levels of MMP8 (matrix metalloproteinase 8 /neutrophil collagenase), LCN2 (lipocalin-2, also known as neutrophil gelatinase-associated lipocalin, NGAL), LTF (lactotransferrin), PRTN3 (proteinase 3) and FCER1A (receptor for Fc fragment of IgE, high affinity I) was profiled by using droplet digital PCR (ddPCR), a next-generation PCR method, which offers absolute quantification with no need of standard curve and greater precision and reproducibility than currently available qRT-PCR methods (10). Expression levels of these genes were tested for its ability to predict hospitalization using a multivariate analysis.

Materials And Methods

Design

this is a new work from our PREWISE study, which prospectively recruited patients presenting with respiratory infection at a Community Health Centre in Spain (Servicio de Urgencias de Atención Primaria, SUAP, Salamanca) from December 2018 to January 2019. While in a previous article from this study we evaluated transcriptomic signatures for detecting viral infection in these patients (11), in the present manuscript we test other totally different gene expression signatures to predict hospitalization.

Patients and setting: recruited patients met the following criteria: age >45 years, clinical signs of upper or lower respiratory infection according to the physician in charge, and at least one of the following items of the National Early Warning Score (NEWS score) (12): Respiration rate < 11 rpm or $\geq$ 21 rpm, oxygen saturation < 95%, any supplemental oxygen, temperature < 36.0 or > 38.1° C, systolic blood pressure < 110 mmHg or $\geq$ 220 mmHg, heart rate < 50 or > 91 or altered level of consciousness. A total of 129 patients were enrolled, of which 29 were finally excluded from the study (14 of them had incomplete follow up data and 15 showed infections of other source than respiratory one).

Ethics declarations

informed consent was obtained from all individuals. The research complied with all the relevant national regulations and institutional policies and was developed in accordance to the tenets of the Helsinki Declaration, and was approved by the “Comité Ético de Investigación con Medicamentos” of the Instituto de Investigación Biomédica de Salamanca (IBSAL) (code PI 2018 11 138).

Gene expression profiling: 2.5 mL of blood were collected by using PaxGene (BD) venous blood vacuum collection tubes. Total RNA was extracted from blood samples using the PAXgene Blood RNA System (PreAnalytix, Hombrechtikon, Switzerland). The evaluation of concentration and quality was performed by spectrometry (Nano-Drop ND1000, NanoDrop Technologies, Wilmington, DE). Gene expression was quantified by ddPCR (BioRad). Granulocyte genes assessed were MMP8 (reference Hs01029057_m1); LCN2 (reference Hs01008571_m1); LTF (Hs00914334_m1); PRTN3 (Hs01597752_m1) and FCER1A (Hs00758600_m1). Predesigned TaqMan Assay Primer/Probe Sets were employed [FAM labeled MGB probes (MMP8, LCN2 and PRTN3), or VIC labeled MGB probes. (FCER1A, LTF) from Thermo Fisher/Scientific-Life Technologies, Waltham, MA, USA]. cDNA was generated from each sample on a Techne TC-512 thermal cycler (Bibby-Scientific, Staffordshire, OSA, UK) starting from 1000 ng of mRNA by using iScript Advanced cDNA Synthesis Kit (BioRad, cat:1725038). The obtained volume of cDNA (20μL) was further diluted (1/25), and 2.5μL (5 ng of total mRNA) were employed for quantification of target gene expression according to the manufacturer instructions. Briefly, ddPCR was performed using the BioRad QX200 ddPCR system, ddPCR Supermix for Probes (no dUTP), and BioRad standard reagents for droplet generation and reading. End-point PCR with 40 cycles was performed by using C1000Touch Thermal Cycler (BioRad) after splitting each sample into approximately 20,000 droplets. Next, the droplet reader used at least 10,000 droplets to determine the percentage of positive droplets and calculation of copy number of cDNA per nanogram of initial mRNA.

Viral diagnosis

Nasopharyngeal aspirates were tested for influenza A H1, influenza H1N1 2009, influenza H3, influenza B, adenovirus, respiratory syncytial virus, rhinovirus, metapneumovirus, and parainfluenza 1,2 and 3 using the FILMARRAY® Respiratory 2 Panel, Biofire, USA) (13)..

Statistical analysis

For the descriptive analysis of the patients' characteristics, the differences between groups were assessed using the Chi-square test or Fisher's Exact Test for categorical variables. For continuous variables, differences between groups were assessed with the Mann-Whitney U test. A multivariate logistic regression analysis was employed to evaluate the association between gene expression levels and the risk of hospitalization in the next 48 hours following first contact with the family doctor. The potential confounding factors were identified by using a univariate analysis followed by multiple testing correction (false discovery ratio FDR- Benjamini-Hochberg) of the *p*-values (a complete list of the variables considered for this analysis is showed in the supplementary material 1). Those variables yielding FDR/*q*-values < 0.200 were further introduced in the multivariate analysis as adjusting variables for gene expression levels. In the case of the categorical variables, only those with a frequency > 5% were considered for the analysis. The predicted values from the multivariate model were used to calculate the area under the receiver operating curve (AUC), which summarizes its predictive power. Statistical analysis was performed using IBM SPSS Statistics 26.0 (SPSS INC, Armonk, NY, U.S.A). The level of significance was set at 0.05 (2-tailed).

Results

Patients' characteristics

demographic and clinical characteristics of the study subjects stratified by the need of hospitalization are provided in Table 1. Patients who finally were admitted to the hospital were older than those not needing hospitalization. The former showed more frequently an antecedent of a neurovascular disease and/or hypertension. The prevalence of viral infections was similar between groups (64% in the patients needing of hospitalization and 65% in the group not needing it, $p > 0.05$), with no differences between both groups in the profile of viruses causing the respiratory infection (supplementary material 1). Mean blood pressure and O₂ saturation was lower in the hospitalised patients, while they presented with higher heart and respiratory rates. NEWS scores were higher in this group. Treatment received for the current episode of respiratory infection was similar between groups, except that non hospitalised patients received more frequently amoxicillin-clavulanic acid. 76% of patients that were finally hospitalised needed of O₂ at first contact with the Primary Health Center, for 13% in the non-hospitalised group. The four patients of this cohort who finally died had been hospitalised.

Table 1

Clinical characteristics of patients: differences between groups were assessed using the Chi-square test or Fisher's Exact Test for categorical variables. For continuous variables, differences between groups were assessed with the Mann-Whitney U test. Significant differences are shown in bold. COPD: Chronic obstructive pulmonary disease. BMI: Body Mass Index.

		All cohort (100)	Patients needing of hospitalization (25)	Non-hospitalized patients (75)	<i>p</i> <i>value</i>
Characteristics	Age [years; median (IQR)]	81.50 (14.00)	84.00 (14.00)	81.00 (16.00)	0.042
	Gender [male; n (%)]	62 (62.00)	16 (64.00)	46 (61.30)	0.812
	BMI [median (IQR)]	25.60 (5.62)	25.71 (8.18)	25.10 (5.21)	0.541
Comorbidities [n (%)]	Neurovascular Disease	20 (20.00)	10 (40.00)	10 (13.30)	0.004
	Cardiac Disease	30 (30.00)	10 (40.00)	20 (26.70)	0.208
	Obesity	20 (20.00)	6 (24.00)	14 (18.70)	0.564
	COPD	21 (21.00)	7 (28.00)	14 (18.70)	0.321
	Asthma	5 (5.00)	2 (8.00)	3 (4.00)	0.427
	Diabetes Mellitus	15 (15.00)	3 (12.00)	12 (16.00)	0.628
	Lipidemia	46 (46.00)	12 (48.00)	34 (45.30)	0.817
	Hypertension	58 (58.00)	20 (80.00)	38 (50.70)	0.010
	Chronic kidney Disease	2 (2.00)	1 (4.00)	1 (1.30)	0.409
	Chronic Liver Disease	1 (1.00)	0 (0.00)	1 (1.30)	0.562
	Biliary Disease	1 (1.00)	0 (0.00)	1 (1.30)	0.562
	Cancer	12 (12.00)	4 (16.00)	8 (10.70)	0.477
	Neurodegenerative Disease	20 (20.00)	5 (20.00)	15 (20.00)	1.000
	Autoimmune Disease	5 (5.00)	2 (8.00)	3 (4.00)	0.427
	Other Diseases	18 (18.00)	6 (24.00)	12 (16.00)	0.367
Vaccination [n (%)]	Influenza Vaccine	70 (70.00)	21 (84.00)	49 (65.30)	0.078
	Pneumococcus Vaccine	55 (55.00)	14 (56.00)	41 (54.70)	0.908
Measures at patient recruitment	Temperature [Celsius; median (IQR)]	38.00 (1.40)	37.40 (1.60)	38.10 (1.40)	0.104
	Mean blood pressure [mmHg; median (IQR)]	91.67 (17.83)	81.67 (20.67)	93.33 (16.67)	0.007
	Heart rate [bpm; median (IQR)]	94.00 (26.00)	100.00 (34.00)	90.00 (20.00)	0.037
	Respiratory rate [bpm; median (IQR)]	24.00 (10.00)	28.00 (9.00)	22.00 (12.00)	0.003
	Supplemental oxygen [n (%)]	29 (29.00)	19 (76.00)	10 (13.30)	< 0.001
	Capillary blood glucose [mg/dl; median (IQR)]	130.00 (38.00)	137.00 (39.00)	128.00 (41.00)	0.119
	Oxygen Saturation [%; median (IQR)]	93.00 (6.00)	89.00 (5.00)	93.00 (5.00)	< 0.001
	Glasgow Scale [median (IQR)]	15.00 (0.00)	15.00 (0.00)	15.00 (0.00)	0.539
	NEWS Score	6.5 (4.75)	9.00 (4.00)	5.00 (5.00)	< 0.001
	Positive respiratory virus test	65 (65.00)	16 (64.00)	49 (65.30)	0.904
Antibiotic treatment for current infection [n (%)]	Quinolone	13 (13.00)	2 (8.00)	11 (14.70)	0.391
	Cephalosporin	2 (2.00)	0 (0.00)	2 (2.70)	0.409
	Amoxicillin	6 (6.00)	1 (4.00)	5 (6.70)	0.627
	Combination of Amoxicillin - Clavulanic Acid	11 (11.00)	0 (0.00)	11 (14.70)	0.042

		All cohort (100)	Patients needing of hospitalization (25)	Non-hospitalized patients (75)	<i>p</i> . value
	Macrolides	7 (7.00)	0 (0.00)	7 (9.30)	0.113
	Combination of antibiotics	5 (5.00)	1 (4.00)	4 (5.30)	0.791
	Not detailed Antibiotic Treatment	8 (8.00)	2 (8.00)	6 (8.00)	1.000
Outcome	Exitus [n (%)]	4 (4.00)	4 (16.00)	0 (0.00)	< 0.001

Gene expression levels in patients needing of hospitalization vs those who did not need to be hospitalised

levels of MMP-8, LCN-2, PRTN-3 and LTF were higher in those patients finally admitted to the hospital, while, on the contrary, levels of FCER-1A were lower (figure 1).

Multivariate logistic regression analysis to predict hospitalization: univariate analysis revealed that all the granulocyte related genes predicted need of hospitalization (MMP8, LCN2, PRTN3, LTF, FCER1A) (supplementary material 2). As shown in Table 2, multivariate analysis demonstrated that, after adjusting by potential confounding factors, all the genes still predicted risk of hospitalization, with ORs even higher than that showed by the NEWS score for ruling in (MMP8, LCN2, PRTN3, LTF) or ruling out hospitalization (FCER1A). The ratio between expression levels of PRTN3 and FCER1A showed the strongest association with the need of hospitalization: (8.36 [2.02 -34.52], 0.003) (OR [CI-95%, *p*]).

Table 2
Multivariate analysis to predict hospitalization. Gene expression values were introduced in the analysis as Napierian

	OR	CI95%	<i>p</i>	OR	CI95%	<i>p</i>	OR	CI95%	<i>p</i>	OR	CI95%	<i>p</i>	OR
NEWS	1.40	1.12	1.75	0.003	1.45	1.16	1.80	0.001	1.51	1.19	1.90	0.001	1.46
Neurovascular disease	3.84	1.05	14.01	0.042	4.13	1.13	15.10	0.032	2.50	0.61	10.26	0.204	2.53
Hypertension	4.87	1.19	19.95	0.028	4.98	1.20	20.66	0.027	2.15	0.55	8.47	0.273	3.59
Age	1.01	0.95	1.07	0.821	1.01	0.95	1.08	0.691	1.02	0.96	1.09	0.505	0.99
MMP8	1.75	1.10	2.79	0.018									
LCN2					2.19	1.22	3.92	0.009					
FCER1A									0.33	0.16	0.69	0.003	
PRTN3													2.17
LTF													
PRTN3/ FCER1A													1.7

AUROC analysis to predict hospitalization

when the multivariate models were tested for their ability to differentiate between hospitalized and non-hospitalized patients using AUCs, the ratio between PRTN3 and FCER1A yielded the highest AUC from all the genes or potential gene ratios when compared to the AUC obtained from the model not including neither individual gene expression levels or gene expression ratios (figure 2).

Discussion

Our results evidenced that the hyperexpression of MMP-8, LCN2, PRTN3, LTF and the hypo-expression of FCER1A in blood is an early predictor of complicated outcome in patients with a respiratory infection acquired at the community. Expression levels of these genes is known to be altered in the context of other kinds of severe respiratory infections. Hyper-expression of MMP-8 and LTF is a signature of ventilator-associated pneumonia (14) (8). MMP-8 correlate also with disease severity in patients with lower respiratory tract infections of viral origin (7) (15). Scicluna B *et al* identified MMP-8 and LCN-2 as part of a 78-gene expression signature of severe community-acquired pneumonia (16). In turn, hyper-expression of LTF, LCN-2 and PRTN3 has been observed in hospitalized patients due to SARS-CoV-1 or SARS-CoV-2 viral infections (17) (18) (19). FCER1A is constitutively expressed in mast cells and basophils and mediates transmission of stimulatory signals upon engagement of IgE-bound allergens (20). Hypo-expression of FCER1A has been repeatedly described in severe infection (6) (21), but its biological implications are unknown.

While the studies evidencing the link between expression levels of these genes and the severity of an infection have been developed at the hospital, our study is the first conducted in a pre-hospital setting, being pioneer in evidencing that this transcriptomic signature involving MMP-8, LCN2, PRTN3, LTF and FCER1A is already altered in the early moments of the disease, at the onset of the symptoms. Early and accurate detection of patients with respiratory infection at risk of deterioration could help to improve outcome of these patients, by accelerating transfer of the patient to the hospital, where further complementary tests and

specific vital/organ support can be administered. The multivariate analysis evidenced that the PRTN3/FCER1A transcriptomic ratio was the gene combination yielding the best results to predict hospitalization, outperforming NEWS. While calculation of NEWS implies scoring several items (some of them showing important inter-observer variations, such as the level of consciousness) (12), gene expression quantification could inform on the prognosis of the patient in a more objective and reproducible manner. Nonetheless, the quantification of gene expression has classically represented a major challenge for translating transcriptomic biomarkers into the clinical practice. New technologies which allows rapid quantification of mRNA transcripts, such as loop-mediated isothermal amplification (LAMP) (22), along with the implementation of laboratories specifically designed to respond to the necessities of family doctors, will facilitate application of these kind of biomarkers to guide clinical decisions in primary care (23).

Finally, a limitation of our study is the limited sample size of our cohort, and the over-representation of respiratory infections of viral origin. Another limitation is that the study was developed before the current COVID-19 pandemics. Further studies recruiting larger cohorts with a more balanced composition of bacterial and viral infections (including SARS-CoV-2) are needed to confirm the predictive performance of the PRTN3/FCER1A ratio.

In conclusion, the gene expression ratio between PRTN3 and FCER1A could represent a useful test to early identify those patients with respiratory infection at risk of deterioration in extra-hospital settings.

Declarations

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Author Contributions.

CHR, JFBM and LGO designed the study. CHR and RA coordinated the development of the study. MMH, MPVA, JANB, MMB, MMRC and the PREWISE study group were on charge of patients' recruitment and sample collection. AO and CD developed the laboratory works. CHR and RA filled in the database. RA, AdF and JFBM analysed the data and drafted the manuscript. RA and AdF drafted the figures. All authors interpreted the results, edited and revised the manuscript and read and approved the final version of the manuscript.

Additional Information:

Competing interests: the authors declare no competing interests.

Data Availability Statement: the steering committee of the PREWISE Investigators Group will consider data sharing upon reasonable request. Requests should be addressed to the corresponding author.

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Figures

Figure 1

Granulocyte`s gene expression levels in patients needing of hospitalization vs those who did not need to be hospitalised. Results are provided as copies of cDNA/ng of initial RNA.

Figure 2

AUROC analysis to predict hospitalization based on the logistic regression models including or not the PRTN3/FCER1A gene expression ratio.

Supplementary Files

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- [7Supplementarymaterial.pdf](#)