Th17 lymphocytes and Interleukin-17A during the course of severe community acquired pneumonia, comparison with etiology and outcome

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ABSTRACT

Objective: Observational study of patients diagnosed with severe community acquired pneumonia (sCAP) carried out to evaluate levels of interleukin 17A (IL-17A) and T helper 17 (Th17) lymphocyte count in peripheral circulation and bronchoalveolar lavage fluid (BALF) in the early course of sCAP of different etiology and to compare them with patient's characteristics and outcome.
Material and methods: Cohort of 74 patients with sCAP was analyzed and respective microbial etiology established. According to pathogens, 3 subgroups of patients were created: bacterial, viral and mixed etiology. Th17 count and IL-17A levels were measured using flow cytometry and ELISA in peripheral blood and BALF. Data were compared with respect to etiology and their correlation with 30- and 90-day mortality was statistically analyzed.
Results: There was no statistically significant correlation in Th17 count and IL-17A levels in blood and BALF between etiological subgroups of CAP and no correlation was found with respect to measured parameters and 30- and 90-day mortality. Nevertheless, increased Th17 cell count and IL-17A levels in peripheral blood, but not in BALF, in the early course of sCAP are correlated with increased relative risk of death from sCAP. Other factors increasing relative risk of death in patients with sCAP found in our cohort were male sex and advanced age.
Conclusions: Systemic Th17 count and IL-17A levels in the early course (up to 7 days from admission) of sCAP may be correlated with severity and outcome of sCAP.

KEYWORDS
severe community acquired pneumonia (sCAP) – Th17 lymphocytes – Interleukin-17A

SOUHRN

Moravec M., Nejtek T., Ibrahimová M., Zazula R., Müller M.: Th17 lymfocyty a interleukin-17A v průběhu těžké komunitní pneumonie, srovnání s etiologií a výsledkem

Cíl: Observační studie pacientů diagnostikovaných s těžkou komunitní pneumonií (sCAP) sledovala hladiny interleukinu-17A a počtu T helper 17 (Th17) lymfocytů v periferní cirkulaci a tekutině z bronchoalveolární laváže (BAL) v časném průběhu komunitní pneumonie různé etiologie a porovnala je s charakteristikami pacientů a klinickým výsledkem.
Materiál a metody: Kohorta 74 pacientů s těžkou komunitní pneumonií byla analyzována s identifikací jednotlivých původců pneumonie. Podle etiologie byli pacienti rozděleni do tří skupin: bakteriální, virové a smíšené etiologie. Počet Th17 lymfocytů a koncentrace IL-17A byly měřeny s využitím průtokové cytometrie a metody ELISA v periferní krvi a tekutině z BAL.
Data byla porovnána podle etiologie sCAP a statistickou analýzou stanovena jejich korelace s 30- a 90denní mortalitou.
Výsledky: Statistická korelace mezi počtem Th17 lymfocytů a koncentrací IL-17A v krvi ani v tekutině z BAL s 30- a 90denní mortalitou nebyla prokázána. Nicméně, zvýšený počet Th17 lymfocytů v periferní cirkulaci, nikoli však v tekutině z BAL, v časném průběhu sCAP koreloval se zvýšeným relativním rizikem úmrtí. Dalšími faktory zvyšujícími relativní riziko smrti byl věk a mužské pohlaví.
Závěr: Hladiny Th17 a IL-17A v systémové cirkulaci v časném průběhu sCAP (v prvních 7 dnech od diagnózy) mohou korelovat s tíží a mortalitou sCAP.

KLÍČOVÁ SLOVA
těžká komunitní pneumonie (sCAP) – Th17 lymfocyty – interleukin-17A

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INTRODUCTION

Community acquired pneumonia (CAP) is one of the leading causes of death worldwide. According to the data from Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community Acquired Pneumonia (REMAP – CAP) platform the annual death toll was estimated at 3 million in 2016. Interestingly, pneumonia as a syndrom itself causes 50% of all cases of sepsis and septic shock [1]. The economic burden of its treatment is enormous and widespread use of antibiotics as a first line treatment is responsible for collateral phenomenon of increasing microbial resistence. The incidence of CAP varies according to different sources between 500–2500 cases per 100000 [2–4]. For developed European countries we can take as a qualified guess for incidence and mortality of CAP recent data (2015) from Germany. The study showed incidence of CAP in adults older then18 years as 1,054 cases per 100,000 person-years of observation. In adults aged 16 to 59 years, incidence was 551 (with a hospitalization rate of 17%). In adults aged more than 60 years, the respective incidence was 2,032 (with a hospitalization rate of 52%). High mortality of hospitalized CAP in adults older than 18 was observed in-hospital (18.5%), at 30 days (22.9%) and at one-year (44.5%) after CAP onset. Mortality was more than double in older adults in comparison to younger patients [5].

CAP, defined as a lung infection contracted outside hospital settings, is diagnosed using clinical (acute onset of fever, dyspnea, cough, pleuritic chest pain, rales) and radiological (abnormal chest radiograph or CT scan with either lobar, multilobar consolidation or interstitial changes) findings. Severe community acquired pneumonia (sCAP) is subset of CAP (about 10–20% of all CAP) with significantly higher morbidity and mortality requiring hospital and often Intensive Care Unit (ICU) admission. The mortality rate for sCAP is estimated in the range between 16-50% [6–8]. For the diagnosis of sCAP, the most commonly used criteria are those of Infectious Diseases Society of America/ American Thoracic Society (IDSA/ATS) 2007 guidelines for sCAP stating that CAP is determined as severe when fulfilling 1 major (out of 2) or 3 minor (out of 9) criteria published in the document [9].

Together with clinical and radiological findings, numerous laboratory parameters are being used to support diagnosis of CAP, to guide clinical management and to predict severity of the disease and its outcome. Although generally accepted definition of CAP presumes immunocompetent host with acute pulmonary infection, interindividual differences in immune system among patients (age, vaccination etc.), variable genetic makeup of innate and adaptive immunity in population and potential subclinical immune challenges prior to contraction of pneumonia make immunological studies in the course of CAP very intriguing tool for personalized approach to clinical management. Recently, thanks to extensive experimental and clinical research in immunology, new elements of immune system emerged which can be used alongside common parameters, i.e. white blood cells (WBC), neutrophils, lymphocytes, immunoglobulins etc., to precise our prognostic abilities and improve patients' outcomes by guiding conventional and immunomodulatory therapy when available and appropriate.

Such parameters with relevance to sCAP seems to be, apart from many others, CD4+ T helper 17 (Th17) lymphocytes and its signature cytokine, interleukin-17A (IL-17A) [10–13].

Th17 cells is a subset of Th CD3+/CD4+ and together with Th1 and Th2 are part of the family of T helper lymphocytes. Th17 were discovered in 2005 and their role in immunity is intensively studied. Th17 reside predominantly in the lamina propria of the mucosa. Their main function is protecting mucosal barrier against invading pathogen and thus are important players in defence mechanisms against acute infections including pneumonia. However, if the regulatory mechanisms fail to control their primary function, they can become immunopathogenic and are involved in inflammatory pathways of some autoimmune disorders and chronic inflammatory diseases [14,15]. Th17 produces cytokines IL-17 and IL-22.

IL-17A, member of IL-17 cytokine family IL-17A-F, is proinflammatory cytokine which is produced by many cellular components of immune system apart from Th17 cells. These are gamma/delta T cells, cytotoxic CD8+ T lymphocytes, natural killer T cells (NKT), mucosal-associated invariant T (MAIT) cells, innate lymphoid cells (ILC), and also neutrophils. IL-17 plays essential roles in protecting the host lung from bacterial and fungal infections and in maintaining the barrier integrity of the lung epithelial mucosa [16–19]. Its main function is induction of granulocyte colony – stimulating factor (G-CSF) and chemokines, which promotes neutrophil accumulation and activation at the infected site. Moreover, together with IL-22, IL-17 increases the expression and release of antimicrobial peptides, e.g. defensins and lipocalin 2. Both mechanisms are responsible for subsequent microbial clearance from invading pathogen. On the other hand, IL-17 can activate other inflammatory pathways and may play a detrimental role in autoimmune diseases, such as asthma or allergic pneumonitis, for which it became a target for immunotherapy. Th17 activation is downregulated by many different pathways, among others by T regulatory lymphocytes (T reg) and IL-23 [14, 20].

Primary aim of this study was to evaluate selected parameters of cellular immunity and cytokine response and their dynamics in peripheral blood and in bronchoalveolar lavage fluid (BALF) and to compare them with clinical characteristics of patients with sCAP. By thorough analysis of the results find out, whether these

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parameters may predict clinical course and outcome of sCAP.

Secondary aim was to evaluate potentially different patterns of Th17/IL-17A immune response with respect to individual pathogens causing sCAP. The change in microbiological landscape for CAP during Coronavirus Disease 2019 (COVID-19) pandemic coinciding with the study timeframe enable us to compare atypical/viral COVID-19 assosciated sCAP with other sCAP pathogens.

And the tertiary objective of the study was to test feasibility and clinical applicability of expanded immunological screening of peripheral blood and bronchoalveolar lavage fluid for the clinical management of severe pulmonary infections.

Table 1. IDSA-ATS sCAP criteria

Minor criteria
Respiratory rate ≥ 30 breaths/min
PaO_2/FiO_2 ratio < 250 torr
Chest X-ray: Multilobar infiltrates
Confusion/desorientation
Blood urea nitrogen > 20 mg/dL
Leukopenia (WBC < 4000 cells/mm^3)
Thrombocytopenia (platelet < 100 000 mm^3)
Hypothermia (core temperature < 36 °C)
Hypotension (Systolic blood pressure < 90 mmHg) requiring aggressive fluid resuscitation
Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors

METHODS

Study protocol and population

Single centre prospective observational study was carried out in the ICU of The Department of Anesthesiology and Resuscitation of Thomayer University Hospital in Prague, Czech Republic from March 2020 to August 2023 and was approved by the Ethical Committee of the Institute for Clinical and Experimental Medicine and the Thomayer University Hospital. Adult patients (> 18years) diagnosed with sCAP according to IDSA/ATS criteria were included (Table 1). Exclusion criteria were as follows: moribund patient not expected to survive more than 24 hours from admission, patients deemed to contract pneumonia in health care settings (HCAP), patients with known immunodeficiency, active tuberculosis, patients with cystic fibrosis.

All patients received standard treatment according to national and international guidelines for the treatment of sCAP and time relevant recommendations for COVID-19 pneumonia management. Data collection and clinical characteristics were recorded according to study protocol. Whenever possible, informed consent was sought from the patients or their next of kin. On admission to ICU (time T0), predefined set of microbiological, laboratory and radiological investigations was done according to study protocol. The same procedure was repeated from day 1 (D1) till day 7 (D7) of ICU or hospital stay. Th17 count in peripheral blood and IL-17A in serum were measured on D1, D3 and D7 following admission to ICU. Together with laboratory tests, all relevant clinical variables were measured and all cause mortality at day 30- and 90-day were recorded. Patients' co-morbidities were assessed and thoroughly documented.

On D1, when clinically appropriate, bronchoalvelor lavage was performed using flexible bronchoscope, three 40 ml aliquots of saline were instilled and then gently aspirated from the area corresponding with consolidation found on chest X-ray or in case of interstitial pattern of pneumonia from the right middle pulmonary lobe. First aspirated BALF was used for culture and Polymerase Chain Reaction (PCR) investigation, 2 remaining aspirates were mixed and sent immediately for immunological analysis into the lab.

Control group of healthy volunteers comprised of 20 subjects with no evidence of acute infection or inflammatory process and noknown immune disorder. Peripheral blood Th17 cells count and serum concentration of IL-17A was investigated as one-off measurement in all of them.

Microbiology studies

Microbial pathogen investigation included RT-PCR (Real-time PCR) testing from nasopharyngeal swab, tracheal aspirate or BALF using commercial multiplex kit for respiratory pathogens, single RT-PCR tests for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or respiratory viruses kit for Influenza A and B, SARS-CoV-2 or Respiratory Syncytial Virus (RSV) combined. All tests were performed at T0 or D1. Moreover, 2 sets of blood cultures were drawn at the time of admission to ICU, tracheal aspirate or sputum were obtained for culture and sent to microbiology for testing. And finally, urinary antigen tests for Legionella pneumophila and Streptococcus pneumoniae were done on admission to ICU. Definitive diagnosis of pathogen was made by combination of the test results and clinical judgment of infectious disease specialist/microbiologist and senior investigator.

Immunology

Flow cytometry analysis

Flow cytometry was used to identify and quantify Th17 cells based on specific surface marker CD4 on T cells and intracellular cytokine IL-17A. The cells were analyzed using a DxFlex flow cytometer (Beckman

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Coulter). All reagents used were purchased from BD Biosciences. For each sample, a minimum of 100,000 lymphocyte-gated events were acquired and analyzed using CytExpert software (Beckman Coulter). The gating strategy was based on the selection of single-cell cell populations and gating CD3+ T cell populations. From this population, we expressed the percentages of positive CD4+ IL-17A+ cells.

IL-17A ELISA

The Human Interleukin-17A (IL-17A) High-Sensitive Enzyme-Linked Immunosorbent Assay (ELISA) was used to measure the concentration of extracellular IL-17A according to the manufacturer's instructions (ThermoFisher Scientific). The assay utilizes a sandwich enzyme immunoassay technique for the quantitative measurement of IL-17A in pg/mL. Serum and BAL samples were collected from a cohort of participants and stored at -80 °C until analysis. ELISA was performed using a DSX instrument (Dynex Technologies). Absorbance was measured at 450 nm, and IL-17A concentrations in samples were determined by interpolation from the standard curve using DSX software.

Statistics

Unless specified in text otherwise, continuous data are presented as median (1st quartile-3rd quartile), categorical data are displayed as frequency/percentage. For comparison of non-parametric data Wilcox/Kruskal-Wallis' test was used. For post-hoc analysis, Wilcoxon rank sum test with continuity correction was performed. For the discrete data comparison we used Chi-squared test. Pearson correlation analysis was used for evaluation of two quantitative variables correlation. The impact of selected variables on survival was analyzed using Cox's regression analysis of survival. P value ≤ 0.05 was considered as statistically significant. For all statistical analyses software R 4.3.3 (The R Foundation, Vienna, Austria) with build-up R-Studio 2024.04.0+735 (Posit Software, PBC, Boston, MA, USA) was used.

RESULTS

A total of 74 patients with the diagnosis of sCAP were included in the study out of 80 recruited by inclusion criteria. 5 excluded patients were found having different diagnosis – non pulmonary sepsis, pulmonary edema or heart failure. One patient was excluded for ongoing hematological malignancy. The majority of patients were male (54M vs 20F). The average age of patients was 64.9 years.

46 patients had SARS-CoV-2 associated pneumonia, 28 non COVID-19 sCAP. For statistics and comparisons of the data the study population was divided in 3 pathogen groups: viral (38 SARS-CoV-2, 1 influenza A), mixed viral and bacterial pneumonia (11 patients, 8 with SARS-CoV-2, 3 of other viral etiology) and finally, bacterial pneumonia (20 patients). In 4 patients the causing pathogen was unknown.The pathogens of sCAP are displayed in Table 2. Mortality according to etiology on day 30 and 90 post admission to ICU is shown in Table 3.

Table 2. The pathogens of Scap

Pathogen	N (%)
SARS-CoV-2	46 (51)
Staphylococcus aureus	10 (11)
Streptococcus pneumoniae	7 (8)
Legionella pneumophila	5 (5)
Haemophilus influenzae	3 (3)
Klebsiella pneumoniae	3 (3)
Streptococcus pyogenes	3 (3)
Enterobacter cloacae	2 (2)
Influenza A	2 (2)
Streptococcus agalactiae	2 (2)
Acinetobacter sp.	1 (1)
Escherichia coli	1 (1)
Chlamydia pneumoniae	1 (1)
Morganella morganii	1 (1)
Human metapneumovirus	1 (1)
Parainfluenza	1 (1)
Serratia sp.	1 (1)

Table 3. Overall mortality according to etiology day 30 and 90 post admission

Mortality	Total	Bacterial	Mixed	Viral
30-day	0,36	0,3	0,36	0,38
90-day	0,49	0,4	0,45	0,54

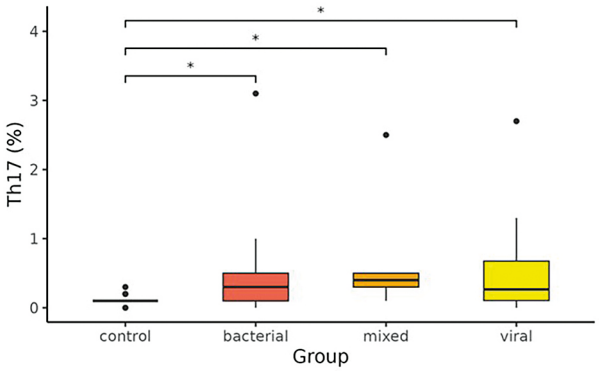

Figure 1. Th17 count in periferial blood (% of total count of T-lymphocytes)
Comparison of control group with values in study groups on Day 1. Star indicates statistical signifikance.

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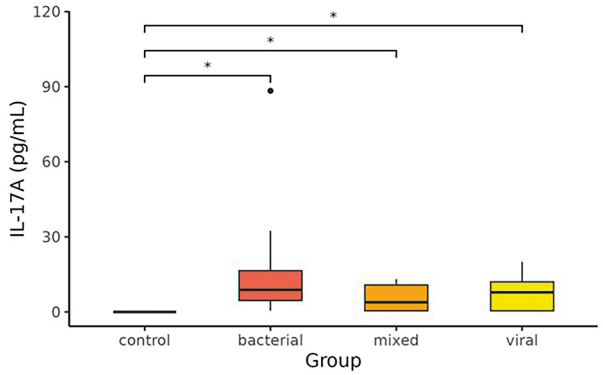

Figure 2. IL-17A serum concentration (pg/mL)
Comparison of control group with values in study groups on Day 1. Star indicates statistical significance.

When compared to control group, Th17 subset counts (% of T lymphocytes) in peripheral blood (Figure 1) and IL-17A serum levels (pg/mL) (Figure 2) showed increased activation throughout T0 to D7.

Th17 counts in peripheral blood on D1, D3 and D7 and their respective values in different pathogen groups is shown in Table 4.

Table 4. Th17 count in peripheral blood (% of total count of T-lymphocytes)

Group	Day 1	Day 3	Day 7
Bacterial	0.85 (0.23–1.62)	0.30 (0.20–0.60)	0.30 (0.10–0.50)
Mixed	0.50 (0.20–2.00)	0.65 (0.48–1.20)	0.40 (0.30–0.50)
Viral	0.31 (0.10–0.60)	0.20 (0.10–0.45)	0.26 (0.11–0.67)
Control	0.10 (0.10–0.10)	–	–

IL17-A serum levels on D1, D3 and D7 according to pathogen group is shown in Table 5.

Table 5. IL-17A serum concentration (pg/mL)

Group	Day 1	Day 3	Day 7
Bacterial	10.05 (4.86–18.24)	8.81 (4.59–16.47)	8.94 (0.90–14.96)
Mixed	4.92 (1.92–10.20)	3.87 (0.47–10.77)	1.90 (0.47–5.17)
Viral	6.26 (0.47–10.55)	7.84 (0.47–12.00)	3.84 (0.47–6.99)
Control	0.00 (0.00–0.00)	–	–

Th17 and IL-17A in BALF was measured on D1 in 29 (Th17), resp. 31 (IL-17A) patients.

The data for Th17 and IL-17A in BALF are shown in Table 6.

Table 6. Th17 lymphocytes count (% of total count of T-lymphocytes) and IL-17A concentration (pg/mL) in bronchoalveolar lavage fluid on Day 1 according to etiology of sCA.

Group	Th17	IL-17A
Bacterial	1.40 (0.05–3.30)	3.61 (1.70–16.98)
Mixed	0.05 (0.00–3.22)	2.14 (0.47–9.03)
Viral	1.41 (0.33–2.40)	3.34 (1.84–7.08)

Statistically significant difference in Th17 count and IL-17A levels between pathogen groups was not found. Analysis of BALF on D1 showed high variability of Th17 activation and IL-17A signaling in all pathogen groups. Nevertheless, we did not observe any correlation between Th17 and IL-17A in BALF and mortality in all pathogen groups. Also, there was no correlation between BALF Th17 counts and IL-17A levels and their respective counterparts in systemic circulation (Figure 3–6).

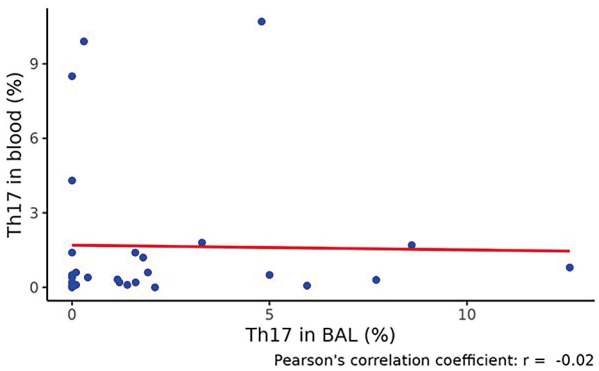

Figure 3. Correlation between Th17 lymphocytes count (% of total count of T-lymfocytes) in blood and in bronchoalveolar fluid

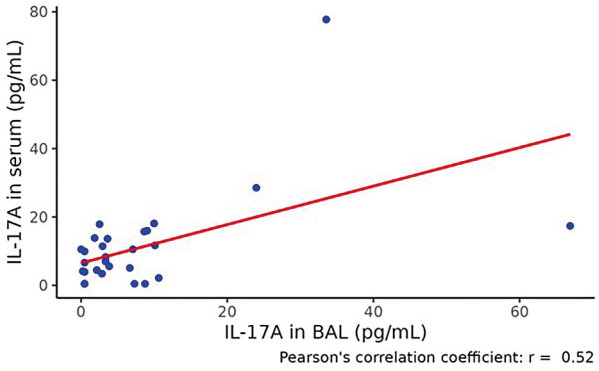

Figure 4. Correlation between IL-17A concentration (pg/mL) in serum and bronchoalveolar fluid

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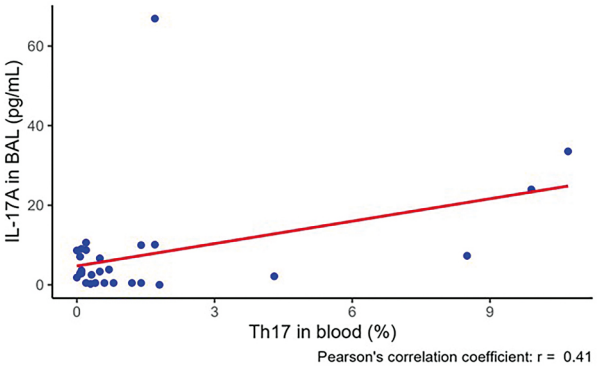

Figure 5. Correlation between Th17 lymphocytes count (% of total count of T-lymfocytes) in blood and IL-17A concentration (pg/mL) in bronchoalveolar fluid

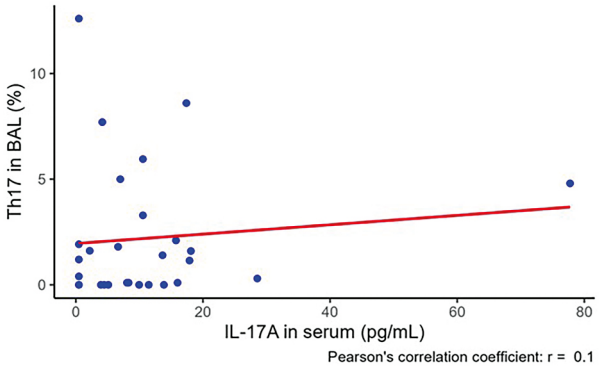

Figure 6. Correlation between IL-17A serum levels (pg/mL) and Th17 lymphocytes count (% of total count of T-lymfocytes) in bronchoalveolar fluid

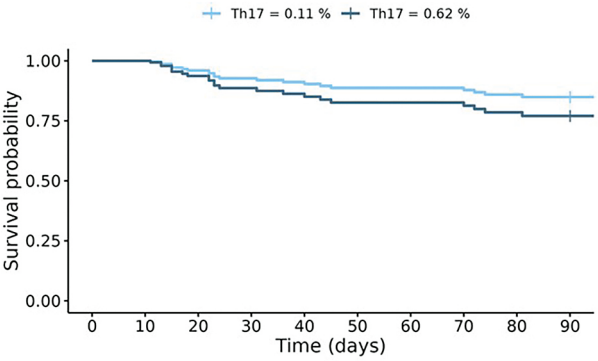

Figure 7. Effect of Th17 lymphocytes count (% of total count of T-lymfocytes) in blood on Day 7 on survival (Cox proportional hazards model)
Th17 values are chosen as 1st quartile and 3rd quartile.

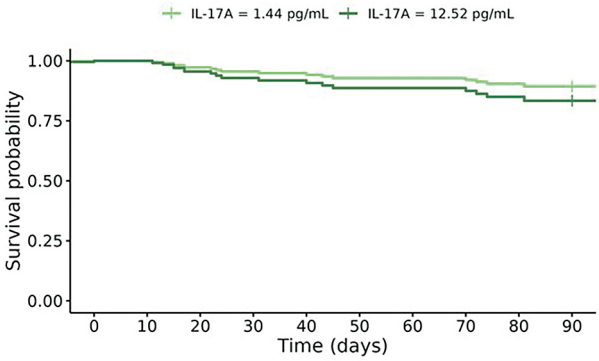

Figure 8. Effect of IL-17A serum levels (pg/mL) on Day 3 on survival (Cox proportional hazards model)
IL-17A concentration values are chosen as 1st quartile and 3rd quartile.

Age, gender, IL-17A serum levels on D3 and Th17 count in peripheral blood on D7 were found as parameters increasing relative risk (RR) of death (Table 7, Figure 7-8).

Table 7. Statistically significant results of Cox survival analysis

Factor	Relative risk of death	p-value
Age	1.06	< 0.001
Male sex	2.6	0.04
Th17 count in blood on Day 7	2.66	0.004
IL-17A serum concentration on Day 3	1.04	0.01

DISCUSSION

There is no doubt that community acqiured pneumonia is very complex inflammatory and immunological process and detailed insight in host/defense interaction and its dynamic in the course of the disease may reveal new aspects in diagnostics and the management of the disease. Nevertheless, the information about diagnostic and prognostic relevance of these immune parameters in clinical settings and their possible impact on patient's outcomes is scarce.

The main finding of the study is evidence of increased activation of Th17 cells in peripheral circulation and marked increase of IL-17A levels in serum of study subjects when compared to control group. Moreover, apart from the expected age and gender correlation with mortality, we have observed in longitudinal analysis of Th17 and IL-17A in systemic circulation statistically significant increased relative risk of death for IL-17A level on D3 and Th17 count on D7 using combined data from study population.

The study showed very high mortality in our cohort. This is even more pronounced in patients with SARS-CoV-2 associated sCAP, the mortality in this group was extremely high overreaching 50% point. The mortality rates are nevertheless in accordance with the data published in the recent literature. Dutch study compared in

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the cohort of more than 10000 patients ICU and in-hospital mortality of ICU patients over 70 years of age for COVID-19 and non-COVID-19 (viral and bacterial) pneumonia. They observed significantly higher ICU and hospital mortality rate for COVID-19 (39.7% and 47.6%) vs bacterial (19.5% nad 28.6%) and non-SARS-CoV-2 viral pneumonia (20,7% and 28,9%) from pre COVID-19 era. Comparison of mortality rate from the same period during COVID-19 pandemics with non-COVID-19 pneumonias showed very similar results [21]. Interestingly, the other study on mortality of over 1800 mechanically ventilated patients for COVID-19 and non-COVID-19 pneumonia did not find significant difference in 90-day mortality between both groups when subjected to complex adjusted analysis of both cohorts (40.2% and 38%). The study cohort though had lower average age (61 years) and included only mechanically ventilated patients [22].

Not surprisingly, the advanced age was found to be a major factor for excessive mortality of sCAP in our cohort. This finding is supported by large number of published studies on sCAP outcome. The obvious explanation for increase vulnerability of older patients to sCAP is immunesenescence, decreased functional reserve and increased number of co-morbidities in this subgroup [23]. There seem to be an interesting point related to findings of our study and possible connection between age and Th17 immunity. According to some investigators, typical pattern of Th17 response in advanced age is increased Th17 levels in elderly patients, absolute or relative in Th cell compartment. Moreover, most of the patients in this age group has decreased T regulatory lymphocytes (Treg) count, which may be an explanation for prolonged Th17 response with limited Treg opposing downregulation of activated Th17 cells in the setting of sCAP in older patients. Elderly thus may be primed to shift the initial protective role of Th17 in the course of the disease to harmful prolonged inflammation of the lungs with consequent unfavorable outcome [24–26]. Female gender was found by most published data as a protective factor for sCAP mortality [27]. There is many possible explanations for this observation, hormonal differences between sexes and increased number of co-morbidities in males being among the leading ones. And again, with respect to Th17 role in host/pathogen interaction in pneumonia, we can find intriguing link between estradiol and Th17. Estradiol seems to curb Th17 activation in the tissues and may be the protective factor against hyperinflammation leading to increased mortality from CAP [25].

Our data showed very low counts of Th17 in peripheral blood of healthy individuals, lower than the most literature sources published recently [24,26]. The explanation may be related to flow cytometry methodology. We were able to quantify the presence of intracellular and extracellular IL-17 in unstimulated human cells and serum, providing a objective snapshot of immune responses in sCAP. However, the use of unstimulated cells brings along the disadvantage of analyzing a lower number of cells. Additionally, unlike other studies using gating strategy related to CD4+ T cells, we express the population of CD4+IL-17+ positive cells (Th17) as a percentage of the total CD3+ lymphocytes (T cells).

Some authors present Th17 cells count as a absolute number of cells rather than a proportionate count. On the other hand quoting percentage number for T cells subset is widely used in the literature on this topic [24,26,28,29]. We felt that proportion of Th17 cells in total T cell count will reflect better potential expansion of this Th cell lineage in the course of sCAP and being aware of low yield of total detected count of Th17 cells we opted for proportionate display of the result in line with majority of published work. The same approach was used in the study conducted by Brunialti group in 2012 in septic patients in comparison with healthy volunteers with respect to immunocyte counts [30].

Nevertheless, we used this method for all analyzed samples including controls throughout the study and therefore we believe the results are objective and presentable. The accuracy of results for IL17A levels is robust, it was measured by commercial ELISA kit and there were strict rules for samples handling and processing.

As expected, in majority of subjects, we found significant activation of both Th17 cells and IL-17A in peripheral circulation in the early course of sCAP in comparison with control group. The findings of IL-17A levels on D3 and Th17 counts on D7 correlating with relative risks of death deserves further attention. They represent one of the hallmarks of our study. From the extensive information about ambivalent roles of Th17 and IL-17A in the setting of acute lung infection we can explain our data as evidence for increasingly harmful role of Th17/IL-17A signalling during the course of the disease process [25, 31]. When initial protective mechanism of Th17/IL-17A response is not downregulated in time, it may cause sustained pro-inflammatory state with tissue damage and increased mortality. Similar results were reported by Brunialti et al. observing sustained elevation of Th17 cells in blood on D7 of treatment in septic patients in non-survivors and its decrease on D7 in survivors. The study included healthy controls and there was over 40% of patients with pulmonary sepsis in septic cohort [30].

Th17 and IL-17A expression in other types of inflammation, infection and sepsis is described in many experimental studies on rodents, mainly in the model of pneumonia or peritonitis induced by cecal ligation. Number of human studies on systemic Th17/IL-17A response in non-pulmonary sepsis is limited. Elevated Th17 and IL-17A were found in patients with burns and this finding was correlated with increased susceptibility to infection and sepsis [32,33]. Similarly, increased levels of IL-17A were observed following myocardial

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infarction with ischemia/reperfusion injury. Costa studied Th derived cytokines in peripheral blood in first two weeks of sepsis diagnosis and found surprisingly low levels of IL-17A [34]. These studies support organ related source of IL-17A, either gamma/delta T cells or Th17 cells increasing IL-17A production induced by inflammatory insult.

The findings of Th17 and IL-17A in BALF deserves further comment. Overall, we did not find any relevance of Th17 counts or IL-17A levels in BALF with the disease course and mortality of studied population. No statistically significant differences were detected even between the pathogen subgroups. And finally, there was no significant correlation between tissue (lung) and systemic (peripheral) blood Th17 count and IL-17A levels and pneumonia etiology or patient's characteristics. The first possible explanation is low number of patients in BALF cohort (31), obvious obstacle for statistical significance. Secondly, collecting BAL fluid for quantitative analysis remains cumbersome. The results depending on the technical skills, appropriate choice of the lung region, the amount of retracted fluid among other factors. Counting cells and measuring substance levels in such samples even following strict BALF protocol for interindividual comparison is questionable. And third possible explanation is that the data are correct and objective, and they only represent differences in patient's phenotypes, as well as pathogen related mucosal response set-up telling us, that the consistent and predictable Th17/IL-17A activation in sCAP at the mucosal site cannot be found. There is interesting point though. Lowest, although not clinically significant Th17 count was found in mixed (viral and bacterial) etiology group. Viral pathogen presumably preceded bacterial superinfection, so we can speculate, that this may be an explanation for depleted mucosal Th cellular compartment when bacterial infection occurs. This difference was not observed in BALF IL-17A levels. Again, speculative, but viable explanation may be other sources of IL-17A found in BALF, which were not affected by previous viral invasion of the mucosa (neutrophils, monocytes, MAIT cells etc.) [35, 36].

Based on our data, we cannot provide sufficient evidence of different pattern of mucosal and systemic response in Th17/IL-17A axis and its correlation with pneumonia course and outcome. The data showed very heterogeneous data from mild to very strong activation and signalling in both compartments (BALF and peripheral blood), but no correlation with either clinical characteristics neither specific pathogen were observed.

To support our findings and for illustration of the complexity of immune response to acute pneumonia, we can extrapolate the data gathered during COVID-19 pandemics. Immunological pathways in SARS-CoV-2 associated pulmonary infection seem to be very heterogeneous. Even in patients with the most severe condition requiring ICU support one can distinguish variable type and intensity of immunological processes. As for T cells, there are patterns typical of strong CD4+ and CD8+ response, which is sustained during the first week of the hospital stay. On the other hand, certain proportion of patients display almost no activation of T helper and T cytotoxic lymphocytes. The increased severity and poor outcome of the disease was observed in both immune profiles [37]. It is likely, that Th17 in peripheral blood would show similarities with other T helper lymphocytes during acute phase of SARS-CoV-2 pneumonia [38] i.e. sustained activation contributing to prolonged inflammatory state of the lungs in some, or low level of Th17 response resembling immunoparalysis in others. Poor outcomes are to be expected among patients from both groups.

Our study has several limitations. First, although intended as prospective observational, we were not able to include all patients fulfilling the inclusion criteria in study period. Main reason was overwhelming critical situation in hospital during COVID-19 pandemic, when many patients escaped enrolment in the study. The other reason was limited availability of immunological studies in weekend periods. Low number of study subjects in the cohort, carried out in single centre is another major limitation. The same applies for low number of BALF investigations, suitability of BALF samples for quantitative analysis and comparative purposes making any reasonable conclusions about mucosal Th17/IL-17A role in host defense very difficult. These factors are responsible for difficulties to assess the potential meaning of differences between mucosal and systemic counts and levels of Th17 and IL-17A in the course of sCAP. And finally, the other important limitation is low number of individual pathogens (especially in bacterial and mixed sCAP group) to observe possible typical patterns related to specific microbial etiology, Th17/IL-17A response and outcome.

Being aware of all these limitations, we were very cautious in interpreting gathered data and formulating objective conclusions. On the other hand, we believe our study produced some relevant and interesting findings.

We have observed and documented significant activity of Th17 cells and increased IL-17A signaling during the early course of sCAP in both, tissue (BALF) and systemic (peripheral blood) compartments. We aimed to contribute to extensive research into the role of Th17/IL-17A in the host defence against the sCAP. We designed our research purely as clinical and thus tested the feasibility of extended immune monitoring in the course of the disease in critically ill patient, bearing in mind the complexity of the nature of immune and inflammatory pathways in such scenario. Unlike majority of similar studies in this field, we have included the patients with different microbial etiology for comparison.

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CONCLUSIONS

Th17 lymphocytes and IL-17A serum levels were significantly elevated from D1 to D7 during the early course of sCAP when compared to healthy controls. Increased serum IL-17A levels on day 3 and Th17 count in peripheral blood on day 7 were correlated with increased relative risk of death in patients with sCAP in our cohort. There was no correlation between mucosal and systemic Th17/IL-17A signaling related to specific pathogen in our cohort. sCAP carries the risk of high mortality, older age and male gender are significant risk factors for poor prognosis and death.

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