

ОЦЕНКА ОТНОШЕНИЯ СУБПОПУЛЯЦИЙ Т-ХЕЛПЕРОВ В РАННЕМ ПОСТТРАВМАТИЧЕСКОМ ПЕРИОДЕ У ДЕТЕЙ

Закиров Р.Ш.^{1,2}, Петричук С.В.¹, Фрейдлин Е.В.¹, Купцова Д.Г.¹,
Янюшкина О.Г.², Карасева О.В.^{1,2}

¹ ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия

² ГБУЗ города Москвы «Научно-исследовательский институт неотложной детской хирургии и травматологии» Департамента здравоохранения города Москвы, Москва, Россия

Резюме. Тяжелая механическая травма является одной из ведущих причин детской инвалидизации и смертности. Дисбаланс гипервоспаления и иммуносупрессии, развивающийся в критическом периоде тяжелой травмы, повышает риск развития инфекционных осложнений и/или полиорганной недостаточности. Целью работы было определение информативных иммунологических критериев оценки риска развития осложнений и прогноза исхода травматической болезни у детей при тяжелой механической травме (ТМТ, ISS ≥ 16 , n = 87) в группах с благоприятным (n = 47) и неблагоприятным исходом (n = 40), а также в зависимости от развития гнойно-септических осложнений (ГСО, n = 16) и синдрома полиорганной недостаточности (СПОН, n = 11). Методом проточной цитометрии проведена оценка соотношения субпопуляций Т-хелперов (Th): регуляторные Т-лимфоциты – CD4⁺CD127^{low}CD25^{high} (Treg), Th 17 типа – CD4⁺CD161⁺ и CD4⁺CD127^{high}CD25^{high}Т-клетки (T127hi) в 1-е, 3-и, 5-е, 7-е, 14-е сутки с момента получения травмы. Группу сравнения составили 34 ребенка с травмой легкой и средней степени тяжести (ЛТ, ISS < 16). Уровни T127hi/Treg и Th17/Treg в первые сутки после травмы у пациентов с ЛТ соответствовали значениям контрольной группы и значительно отличались от группы ТМТ. Для пациентов с ТМТ выявлено выраженное увеличение соотношения Th17/Treg в остром посттравматическом периоде с тенденцией к снижению к 7-14-м суткам после травмы. Для детей с ТМТ обнаружены различия в динамике анализируемых показателей в зависимости от развития осложнений и исхода травматической болезни. Динамика уровня Th17/Treg в остром посттравматическом периоде значительно отличалась у детей с ТМТ при развитии ГСО и неблагоприятном исходе на 7-е и 14-е сутки соответственно. Низкий уровень T127hi/Treg у пациентов с ТМТ в значительной степени связан с развитием ГСО. Несмотря на то, что достоверных отличий анализируемых показателей в группах пациентов в зависимости от развития СПОН выявлено не было, у паци-

Адрес для переписки:

Рустам Шакирович Закиров
ФГАУ «Национальный медицинский исследовательский
центр здоровья детей» Министерства
здравоохранения РФ
119296, Россия, Москва, Ломоносовский пр., 2, стр. 1.
Тел.: 8 (926) 692-70-97.
E-mail: zakirov.rsh@nczd.ru

Address for correspondence:

Rustam Sh. Zakirov
National Medical Research Center for Children's Health
2 Lomonosovsky Ave, Bldg 1
Moscow
119296 Russian Federation
Phone: +7 (926) 692-70-97.
E-mail: zakirov.rsh@nczd.ru

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ентов с СПОН были отмечены более низкие медианные значения для Th17/Treg and T127hi/Treg, чем у пациентов без СПОН начиная с 3-х суток после травмы. Для Th17/T127hi достоверных различий в группе тяжелой травмы в зависимости от развития осложнений и исхода травматической болезни выявлено не было. Результаты исследования свидетельствуют о том, что у детей уровни Th17/Treg и T127hi/Treg могут быть использованы для прогнозирования исхода травматического заболевания и оценки риска развития инфекционных осложнений и синдрома полиорганной дисфункции.

Ключевые слова: дети, тяжелая травма, политравма, отношение субпопуляций T-хелперов, синдром полиорганной недостаточности, прогноз исхода, инфекционные осложнения

T HELPER SUBSETS DURING THE ACUTE POST-TRAUMATIC PERIOD IN CHILDREN

Zakirov R.Sh.^{a, b}, Petrichuk S.V.^a, Freidlin E.V.^a, Kuptsova D.G.^a,
Yanyushkina O.G.^b, Karaseva O.V.^{a, b}

^a National Medical Research Center for Children's Health, Moscow, Russian Federation

^b Institute of Urgent Children Surgery and Traumatology, Moscow, Russian Federation

Abstract. Severe mechanical injury is among the main reasons of disability and mortality in pediatric patients. The imbalance between the states of inflammation and immune suppression during the critical period of post-traumatic injury bears an elevated risk for infectious complications and/or multiple organ failure. The present study aimed to determine the informative immunological criteria in order to evaluate severity and prognosis for clinical outcomes in children from the severe injury group (SInj, ISS \geq 16, n = 87); mild/moderate injury group (MInj, ISS < 16, n = 34), as based on assessment of helper T cells (Th) ratios, i.e., Th17/Treg, T127hi/Treg, and Th17/T127hi. The patients with severe injuries were classified by their outcomes (favorable, n = 47; unfavorable, n = 40), presence of infectious complications (IC, n = 16) and the development of multiple organ failure (MOF, n = 11). Th ratios were studied on the 1st, 3rd, 5th, 7th, 14th day after injury. For the SInj group, a pronounced increase of Th17/Treg ratio in the acute post-traumatic period with a decrease by 14 days was revealed. The indices of T127hi/Treg ratio on the first day for the patients from MInj group corresponded to the values of control group and significantly differed from patients with SInj in the 3rd to 5th day. There are different kinetics of Th subset ratio in peripheral blood of children with severe injuries over time in different groups, as well as with/without MOF, in presence, or absence of infectious complications and different clinical outcomes. Significant differences in T127hi/Treg ratio level were found in group with IC from 1st to 3rd day and from 7th to 14th day. Significant differences in Th17/Treg ratio level were found in IC group (7th day), in MOF group on 14th day post-injury. The patients with MOF had lower median concentrations of Th17/Treg and T127hi/Treg than patients without MOF. The results of the study indicate that the levels of Th17/Treg and T127hi/Treg ratio in children may be used to predict outcome of the traumatic disease and assess the risk of infectious complications and multiple organ dysfunction syndrome.

Keywords: children, severe injury, polytrauma, T helper subsets ratio, multiple organ failure, outcome prediction, infectious complications

Introduction

Severe mechanical injury is one of the leading causes of childhood disability and mortality [4]. Severe injury induces a complex host immune response to tissue damage, a parallel pro- and anti-inflammatory state associated with an increased risk of infectious complications (IC) and/or multiple organ failure (MOF) [2, 6]. A period of pronounced immunosuppression is usually observed,

the pathogenesis of which is largely determined by a decrease in the level of T lymphocytes (Th) in severe trauma [8]. Also, it has been demonstrated that Treg is activated in response to massive spread causing induced injury, downregulation of Th1 responses, and T cell anergy [5]. The quantity of T helper subpopulations, such as regulatory T lymphocytes (Treg) – CD4⁺CD127^{low}CD25^{high} and Th17 lymphocytes (Th17), can be a significant marker in the frequency of the pathological process

and predicting its outcome. Th17 and Treg cells have opposite roles in the development of autoimmune and inflammatory diseases. While Th17 cells promote autoimmunity, Treg cells serve to control it and therefore play a very important role in autoimmune pathogenesis by maintaining self-tolerance and by controlling expansion and activation of autoreactive CD4⁺T effector cells. The control of Th17/Treg balance appears also critical in the development of many diseases, including severe trauma [9]. However, further evaluation is required to determine exact kinetic changes of CD4⁺T cells subsets count post-trauma.

The purpose of this study was to identify informative immunological criteria for the traumatic disease severity and as applicable to children. The identification relies on the assessment of Th subsets ratio – Th17/Treg, T127hi/Treg, and Th17/T127hi.

Materials and methods

The study involved 87 patients (58 boys (66.6%), 35 girls (33.4%); 331 observation sessions) with severe injury (SInj), treated at the Department of Anesthesiology and Resuscitation of the Research Institute of Emergency Pediatric Surgery and Traumatology. We used the laboratory of the National Medical Research Center for Children's Health for laboratory studies, which were prescribed 1 to 5 times, depending on the length of stay of a given child at the ICU. The mean age of the children was 12.0 (5.75–15.0) years (Me (Q_{0.25}-Q_{0.75})). The time options for laboratory studies were the first, third, fifth, seventh and 14th days from the day of injury. The comparison group was comprised of 34 patients (15 boys (44.1%), 19 girls (55.9%); 34 observation sessions) with mild/moderate injury (MInj) treated at the Department of Neurotrauma. The control group was comprised of 80 apparently healthy children, all of them underwent medical examination at the National Medical Research Center for Children's Health. The children were comparable in age and sex: age – 12.41 (4.4–16.2) years (Me (Q_{0.25}-Q_{0.75})); 47 boys (58.7%), 33 girls (41.3%).

Assessing the injury, we relied on the Injury Severity Score (ISS) and the Glasgow Coma Scale (GCS). The outcome of an SInj was assessed with the help of the Glasgow Outcome Scale (GOS) and the Severe Injury Outcomes Scale (OISS) [10]. These scales were applied to assess the condition of the patient at discharge from the hospital.

The patients in our study met the following criteria: severe injury (ISS ≥ 16), aged 1-18 years, admittance to the ICU within 72 hours. Concomitant acute

inflammatory and chronic diseases were a reason for exclusion.

At the first stage, we analyzed the results from the control group, the MInj (ISS 4.0 (4.0-9.0) (Me (Q_{0.25}-Q_{0.75}))) and the SInj group (ISS 26.0 (21.0-29.0) (Me (Q_{0.25}-Q_{0.75}))). At the second stage, we analyzed the two groups from SInj formed with the help of GOS and OISS, the favorable outcome group (SInjfav, n = 47) and the unfavorable outcome group (SInjunfav, n = 40). The distribution into these groups was based on the scores: patients were allocated to the SInjfav group if they scored 4-5 points on the GOS scale and 1-2 points on the OISS scale, and to the SInjunfav group if they scored 1-3 points on the GOS scale and 3-5 points on the OISS scale.

Clinical and laboratory indicators of systemic inflammatory response syndrome and organ failure were evaluated in all patients with severe injury. Organ functioning was assessed daily after admission to the ICU using MODS (Multiple Organ Dysfunction Score) [7]. Patients with severe injury were divided into groups depending on infectious complications (IC n = 16) and the development of MODS (MODS n = 11).

We assessed the absolute cell count of T127hi – CD4⁺CD127^{high}CD25^{high}, Th17 – CD4⁺CD161⁺, Treg – CD4⁺CD127^{low}CD25^{high} and their ratio Th17/Treg, T127hi/Treg, and Th17/T127hi in the patients. Two-platform technology enabled assessment of the quantitative indicators of the subpopulation composition of peripheral blood T lymphocytes. The absolute number of lymphocytes was calculated with the help of a Sysmex XT-2000i hematology analyzer (Sysmex Corporation; Japan). The preparation of samples for cytofluorimetric analysis included incubation of 100 μL of whole blood with 10 μL of monoclonal antibodies tagged with fluorochromes for 20 min in a dark place. The erythrocytes were lysed with BD FACS™ Lysing Solution (BD Biosciences; USA); the duration of incubation therewith in the dark at room temperature did not exceed 10-12 minutes. The resulting samples were analyzed in a Novocyte flow cytometer (ACEA Biosciences; USA). The surface markers used to determine lymphocyte subpopulations were as follows: CD45, IgG1, IgG2a, CD3, CD4, CD25, CD127, CD161 (Beckman Coulter, USA; BD Biosciences, USA; SONY corp., Japan).

We used MS Excel 2016 (Microsoft corp.; USA), Statistica 10 (StatSoft, Inc.; USA) to process the data obtained. The results are presented as a median (Me) and quartiles (Q_{0.25}-Q_{0.75}). Mann-Whitney U test and Kruskal-Wallis test enabled comparison of differences in the attributes. The conclusions were considered significant at p < 0.05 (*).

Results and discussion

Using the nonparametric Kruskal–Wallis test, we compared the differences in Th17/Treg, T127hi/Treg, and Th17/T127hi ratio in children with injury over time in different groups: Control group, Minj and Sinj groups (Table 1, Figure 1). For Sinj group, a pronounced increase of Th17/Treg ratio in the acute post-traumatic period with a decrease to 14 days was revealed groups (Figure 1A). The values of T127hi/Treg and Th17/T127hi in the first day for indicators of patients with MInj correspond to the values of control group and significantly differ from patients with SInj in the 3–5th day and in the 5–14th day after the injury respectively (Figure 1B, C).

Using the nonparametric Mann–Whitney test, we compared the differences in Th subsets ratio in children with severe injury over time in different groups: with and without MOF, with and without IC and outcome groups (Table 1).

Significant differences in Th17/Treg ratio level were found in IC groups – on 7th day, in OISS groups on 14th day from, and no reliable differences in groups with and without MOF throughout the observation period. Significant differences in T127hi/Treg ratio level were found in IC groups from 1st to 3rd day and from 7th to 14th day, in IC and OISS – no reliable differences. Also, there were no significant differences

in the level of Th17/T127hi for all comparison groups in children with severe trauma (Table 1, Figure 2C–F, see 3rd page of cover). Even though the levels of Th subsets ratio in the groups were determined in a wide range of values, patients with MOF had lower median concentrations within from 7th to 14th day for Th17/Treg and from 3rd to 14th day – for T127hi/Treg than patients without MOF (Table 1, Figure 2A, B, see 3rd page of cover). This is due to differences in the kinetics of the levels of Th subsets in the acute post-traumatic period in children. The level of T127hi lymphocytes reach normal values by 5th day, unlike Th17 and Treg, the level of which remains reduced for up to 7–14 days. The patients with MOF and/or with IC had significantly lower median concentrations of Th17 and Treg within 1–7 days after admission to the ICU than patients without MOF/IC (Figure 2, see 3rd page of cover). Zhang et al. demonstrated that the level of Th17 showed increased initially and then decreased in patients with thoracic trauma. The frequency of Th17 was significantly increased in traumatic patients compared to healthy controls on the day after admission [11]. Another studies have shown that on trauma patients found elevated Th17/CD4⁺Treg ratios in trauma patients who developed sepsis, furthermore the ratio of Th17 cells to CD4⁺Tregs was skewed in favor of Th17 cells in non-surviving patients [1, 3].

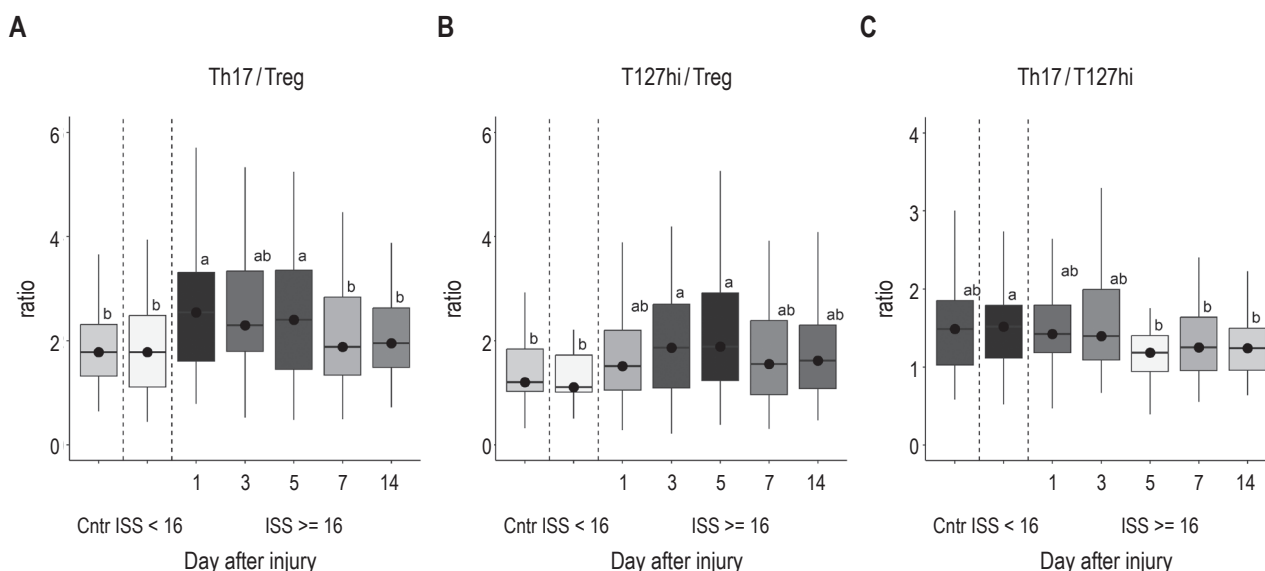


Figure 1. Dynamics of Th17/Treg (A), T127hi/Treg (B), and Th17/T127hi (C) ratio in the critical period of injury in children

Note. Me ($Q_{0.25}$ – $Q_{0.75}$) Min–Max; the significance is represented by letters according to pairwise comparison through the Kruskal–Wallis test; comparison groups: Cntr – control group; ISS < 16 – MInj group; ISS >= 16 – SInj group by day after severe injury.

TABLE 1. DYNAMICS OF Th17/Treg, T127hi/Treg, AND Th17/T127hi RATIO IN THE CRITICAL PERIOD OF SEVERE INJURY IN CHILDREN (Sinj GROUP) IN COMPARATION WITH CONTROL GROUP AND Minj GROUP AND IN Sinj GROUP DEPENDING OF IC, MOF DEVELOPMENT AND OUTCOME PREDICTION OF OISS, Me (Q_{0.25}-Q_{0.75})

Factor		Control	Minj	Sinj, day after injury				
				1	3	5	7	14
n		80	34	68	87	35	74	67
Th17/Treg	ratio c. u.	1.78 (1.32-2.31)	1.78 (1.11-2.48)	2.58 (1.83-3.36)	2.45 (1.82-3.43)	2.47 (1.50-3.43)	1.88 (1.34-2.84)	1.95 (1.49-2.63)
MOF Th17/Treg	N			2.59 (1.61-3.34)	2.52 (1.80-3.61)	2.50 (1.67-3.86)	2.04 (1.36-2.92)	2.07 (1.54-2.72)
	Y			2.45 (2.21-3.57)	2.28 (2.04-2.97)	2.33 (1.13-2.59)	1.45 (1.18-2.08)	1.49 (1.34-1.99)
IC Th17/Treg	N			2.77 (2.09-3.42)	2.57 (1.94-3.75)	2.47 (1.41-3.20)	2.13 (1.46-2.98)*	2.02 (1.53-2.63)
	Y			2.03 (1.65-2.48)	2.24 (1.77-2.65)	3.21 (2.18-4.56)	1.28 (1.00-1.82)*	1.52 (1.17-2.38)
OISS Th17/Treg	F			2.61 (1.60-3.28)	2.27 (1.77-3.44)	2.38 (1.90-3.85)	2.22 (1.27-3.05)	2.20 (1.77-2.92)*
	UF			2.50 (1.90-4.51)	2.65 (1.99-3.29)	2.54 (1.13-2.88)	1.81 (1.39-2.15)	1.58 (1.32-2.46)*
T127hi/ Treg	ratio c. u.	1.20 (1.03-1.84)	1.11 (1.01-1.73)	1.55 (1.08-2.46)	1.87 (1.09-2.73)	1.89 (1.23-2.92)	1.55 (0.96-2.39)	1.62 (1.08-2.30)
MOF T127hi/ Treg	N			1.53 (1.04-2.23)	1.89 (1.13-2.77)	1.90 (1.40-2.95)	1.63 (1.14-2.40)	1.73 (1.15-2.47)
	Y			1.87 (1.23-3.01)	1.20 (0.82-2.14)	1.22 (0.98-1.89)	0.94 (0.83-2.11)	1.27 (0.99-1.71)
IC T127hi/ Treg	N			1.70 (1.16-2.69)*	2.11 (1.13-2.87)**	1.89 (1.25-2.89)	1.70 (1.11-2.44)*	1.78 (1.15-2.47)*
	Y			1.00 (0.82-1.38)*	1.20 (0.83-1.68)**	2.10 (1.11-3.73)	1.09 (0.77-1.46)*	1.26 (0.78-1.40)*
OISS T127hi/ Treg	F			1.70 (1.10-2.34)	1.69 (1.02-2.51)	1.88 (1.44-2.91)	1.67 (1.01-2.38)	2.01 (1.16-2.82)
	UF			1.41 (1.04-2.74)	2.05 (1.18-2.82)	1.89 (1.06-2.89)	1.45 (0.98-2.31)	1.44 (1.05-1.95)
Th17/ T127hi	ratio c. u.	1.49 (1.03-1.85)	1.52 (1.12-1.79)	1.47 (1.21-2.10)	1.40 (1.09-1.99)	1.18 (0.94-1.40)	1.25 (0.96-1.64)	1.24 (0.96-1.50)

Table 1 (continued)

Factor		Control	MInj	SInj, day after injury				
				1	3	5	7	14
n		80	34	68	87	35	74	67
MOF Th17/ T127hi	N			1.48 (1.21-2.10)	1.38 (1.09-1.96)	1.16 (0.91-1.36)	1.25 (0.94-1.58)	1.20 (0.96-1.56)
	Y			1.36 (1.24-1.61)	1.44 (0.95-2.52)	1.27 (1.26-1.45)	1.46 (1.08-1.82)	1.32 (0.99-1.44)
IC Th17/ T127hi	N			1.42 (1.14-2.09)	1.37 (1.07-1.91)	1.18 (0.89-1.33)	1.25 (0.96-1.63)	1.19 (0.91-1.50)
	Y			1.62 (1.44-2.20)	2.03 (1.26-2.56)	1.22 (1.00-1.66)	1.27 (0.97-1.86)	1.32 (1.12-1.53)
OISS Th17/ T127hi	F			1.43 (1.20-1.80)	1.43 (1.10-2.03)	1.27 (0.90-1.52)	1.33 (0.96-1.62)	1.24 (0.96-1.47)
	UF			1.60 (1.26-2.24)	1.29 (1.09-1.86)	1.08 (1.00-1.27)	1.20 (0.96-1.69)	1.24 (0.97-1.51)

Note. Mann–Whitney U test; *, p <0,05; **, p <0,01; comparison groups: MOF group (N, no; Y, yes); Infectious complication (N, no; Y, yes); Outcome (F, favorable outcome; UF, unfavorable outcome); c. u., conventional units.

Conclusions

Therefore, we have characterized and analyzed the dynamics of Th subsets ratio – Th17/Treg, T127hi/Treg, and Th17/T127hi in the critical period of severe injury in children, which may play an important role in the post-traumatic immunosuppression, and thereby the recovery from trauma. The lower-level T127hi/Treg ratio in trauma patients admitted to the ICU is significantly associated with develop the infectious complications and MOF. The lower-level Th17/Treg is significantly associated with develop the infectious complications and outcome of the traumatic disease.

Compliance with ethical standards

The study was conducted in accordance with the Declaration of Helsinki and approved by the Committee on Biomedical Ethics of Institute of Urgent Children Surgery and Traumatology (Protocol No. 2 of 26.05.2020). All study participants signed an informed consent.

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Авторы:

Закиров Р.Ш. — врач клинической лабораторной диагностики клиничко-диагностической лаборатории ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ; научный сотрудник лаборатории иммунологических, цитохимических и биохимических методов исследования ГБУЗ города Москвы «Научно-исследовательский институт неотложной детской хирургии и травматологии» Департамента здравоохранения города Москвы, Москва, Россия

Петричук С.В. — д.б.н., профессор, главный научный сотрудник лаборатории экспериментальной иммунологии и вирусологии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия

Authors:

Zakirov R.Sh., Clinical Laboratory Doctor, Clinical Diagnostic Laboratory, National Medical Research Center for Children's Health; Research Associate, Laboratory of Immunology, Cytochemistry and Biochemistry, Institute of Urgent Children Surgery and Traumatology, Moscow, Russian Federation

Petrichuk S.V., PhD, MD (Biology), Professor, Chief Research Associate, Laboratory of Experimental Immunology and Virology, National Medical Research Center for Children's Health, Moscow, Russian Federation

Фрейдлин Е.В. — лаборант-исследователь лаборатории экспериментальной иммунологии и вирусологии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия

Купцова Д.Г. — младший научный сотрудник, врач клинической лабораторной диагностики лаборатории экспериментальной иммунологии и вирусологии ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия

Янюшкина О.Г. — научный сотрудник отдела сочетанной травмы, анестезиологии и реанимации ГБУЗ города Москвы «Научно-исследовательский институт неотложной детской хирургии и травматологии» Департамента здравоохранения города Москвы, Москва, Россия

Карасева О.В. — д.м.н., профессор, заместитель директора по научной работе, руководитель отдела сочетанной травмы, анестезиологии и реанимации ГБУЗ города Москвы «Научно-исследовательский институт неотложной детской хирургии и травматологии» Департамента здравоохранения города Москвы; заведующая отделением неотложной хирургии и травмы у детей ФГАУ «Национальный медицинский исследовательский центр здоровья детей» Министерства здравоохранения РФ, Москва, Россия

Freidlyn E.V., Research Laboratory Assistant, Laboratory of Experimental Immunology and Virology, National Medical Research Center for Children's Health, Moscow, Russian Federation

Kuptsova D.G., Junior Research Associate, Clinical Laboratory Doctor, Laboratory of Experimental Immunology and Virology, National Medical Research Center for Children's Health, Moscow, Russian Federation

Yanyushkina O.G., Research Associate, Department of Multiple Trauma and Intensive Care Unit, Institute of Urgent Children Surgery and Traumatology, Moscow, Russian Federation

Karaseva O.V., PhD, MD (Medicine), Professor, Deputy Director for Research, Chief of Department of Multiple Trauma and Intensive Care Unit, Institute of Urgent Children Surgery and Traumatology; Head, Department of Emergency Surgery and Trauma in Children, National Medical Research Center for Children's Health, Moscow, Russian Federation

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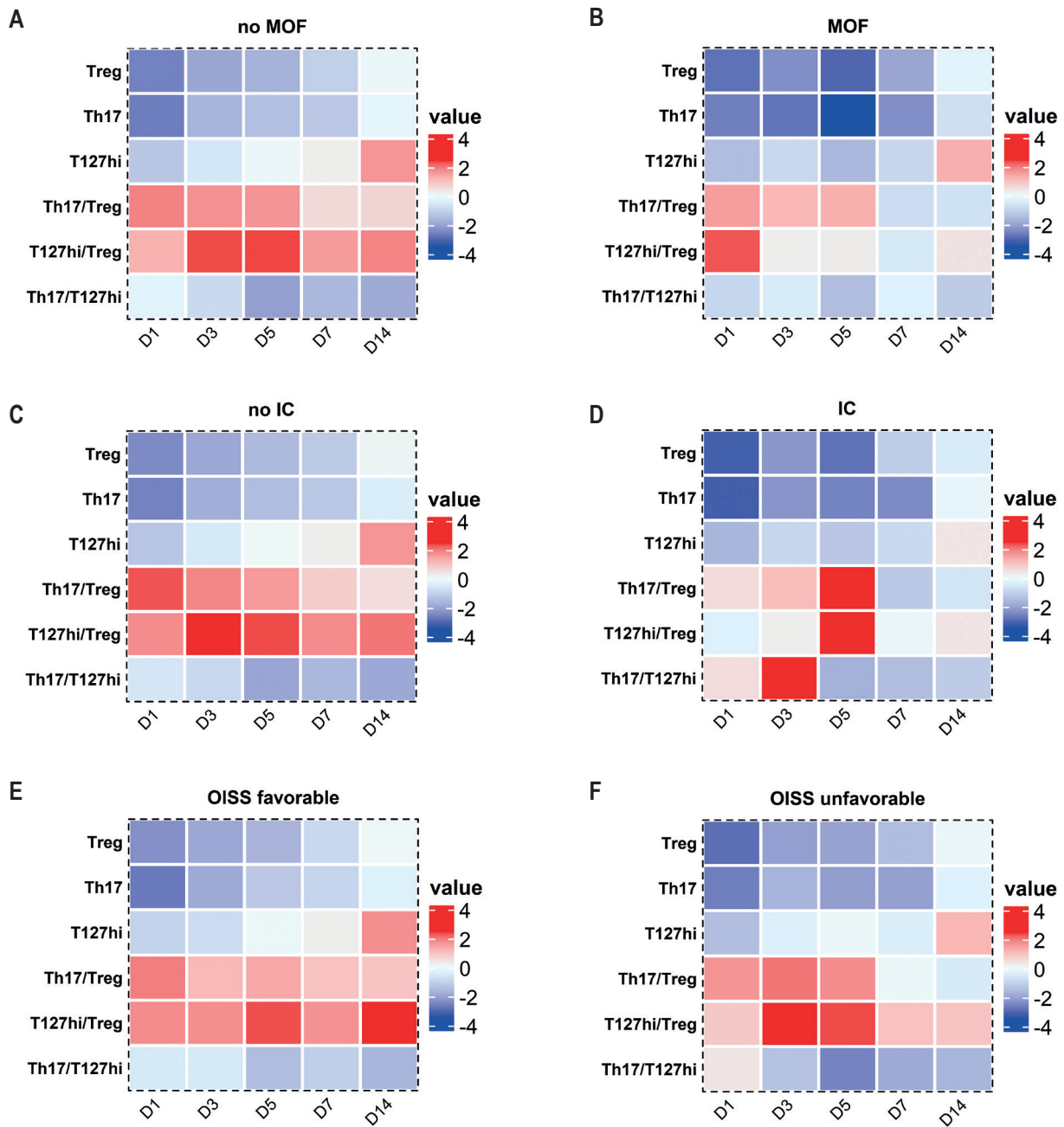


Figure 2. Heat maps show the kinetics of changes in peripheral blood T127hi, Treg, Th17 absolute cell count levels and Th17/Treg, T127hi/Treg, and Th17/T127hi ratio levels in the critical period of severe injury in children depending of MOF (A, B), infectious complication (C, D) development and outcome prediction of OISS (E, F)