Burn-Induced Local and Systemic Immune Response: Systematic Review and Meta-Analysis of Animal Studies

JID Open

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Because burn injuries are often followed by a derailed immune response and excessive inflammation, a thorough understanding of the occurring reactions is key to preventing secondary complications. This systematic review, which includes 247 animal studies, shows the postburn response of 14 different immune cell types involved in immediate and long-term effects in both wound tissue and circulation. Peripheral blood neutrophil and monocyte numbers increased directly after burns, whereas thrombocyte numbers increased near the end of the first week. However, lymphocyte numbers were decreased for at least 2 weeks. In burn wound tissue, neutrophil and macrophage numbers accumulated during the first 3 weeks. Burns also altered cellular functions because we found an increased migratory potential of leukocytes, impaired antibacterial activity of neutrophils, and enhanced inflammatory mediator production by macrophages. Neutrophil surges were positively associated with burn size and were highest in rats. Altogether, this comprehensive overview of the temporal immune cell dynamics shows that unlike normal wound healing, burn injury induces a long-lasting inflammatory response. It provides a fundamental research basis to improve experimental set-ups, burn care, and outcomes.

Journal of Investigative Dermatology (2022) **142,** 3093–3109; doi:10.1016/j.jid.2022.05.004

INTRODUCTION

Burn trauma often induces an overreaction of the immune system, known as systemic inflammatory response syndrome, which can cause damage to surrounding tissues and even distant organs (Farina et al., 2013; Pantalone et al., 2021). Hyperactive inflammation and obstruction of wound healing can lead to excessive scarring (Eming et al., 2014) and psychological distress (Fauerbach et al., 2007). Information on the specific immune cells and inflammatory factors involved in the different phases of burn wound healing in humans is however scattered and incomplete.

Human studies are limited by the absence of baseline values, heterogeneity among cases, and restrictions in (the timing of) blood and wound sampling. Animal experiments, executed in controlled and standardized settings (Abdullahi et al., 2014), could improve our understanding of the mechanisms underlying the burn-induced immune response in humans. Undoubtedly, various genomic and physiological processes of the human response to trauma differ from that of animals, such as signaling pathways, wound contraction, and scar formation (Dahiya, 2009; Seok et al., 2013; Zomer and Trentin, 2018). Nevertheless, animal studies contain valuable information that will improve our understanding of the cellular immune response to burn trauma. In this study, we aimed to identify the immune cells involved in the local and systemic inflammatory response to burn injury in animal models. Ultimately, we anticipate that this review leads to new perspectives in burn care and will support the improvement of treatment for patients.

RESULTS

Study selection, characteristics, and quality

Our search generated 10,733 citations, of which 1,224 were considered relevant during title and abstract screening. From this selection, 111 studies were inaccessible, 247 were included in the systematic review (Figure 1), and 182 were used in meta-analyses (Supplementary Files S1 and S2). An overview of the study characteristics (Figure 2a–g) showed that most experiments were performed on young mice or rats. Full-thickness dorsal injury using hot water was the most common burn technique. It is worth noting that underreporting complicated the assessment of the overall study quality. Risk of bias (RoB) analysis showed that 33.5% of the included studies reported the use of randomization of animals before experimentation (Figure 2h). The majority of studies (94.0%) did not report the use of blinding, and a conflict-of-interest statement was present in 33.9% of the studies, in which four studies reported an actual conflict (Figure 2i and j). Overall, there was no significant indication

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Abbreviations: NLR, neutrophil/lymphocyte ratio; PBD, postburn day; RoB, risk of bias; TBSA, total body surface area

Received 14 February 2022; revised 8 April 2022; accepted 2 May 2022; Accepted manuscript published online 25 May 2022

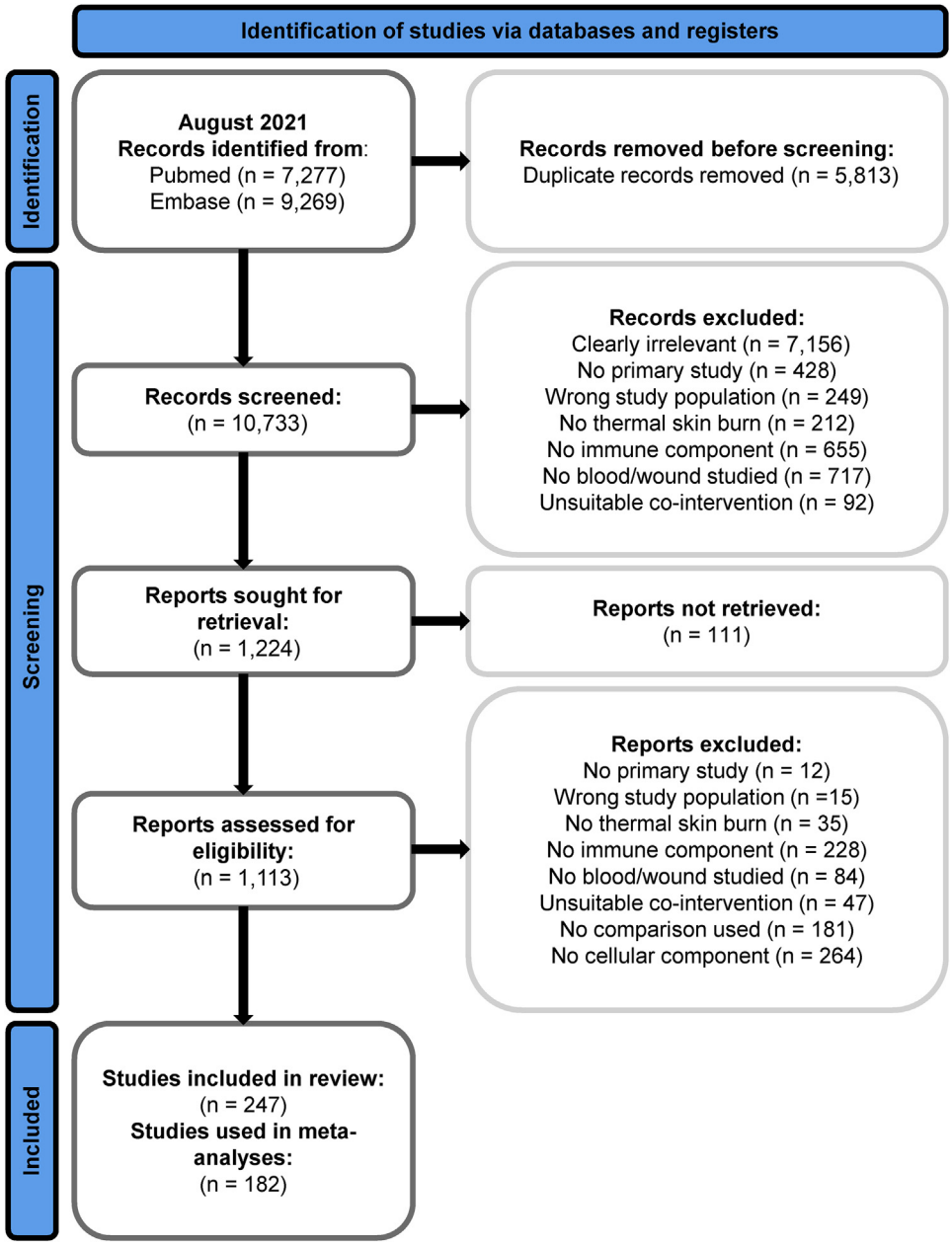


Figure 1. PRISMA flowchart of study identification, screening, and inclusion. Representation of the steps taken to select the relevant studies for the systematic review and meta-analyses (Page et al., 2021). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

of publication bias for the overall outcomes, but we did find a substantial risk of selection and performance bias.

Burn-induced immune response is dominated by innate immune cells

Meta-analyses were performed on outcome measures for which at least five articles were available (Supplementary Table S1). Immune cell counts in blood or wound tissue from burn-injured animals were compared with immune cell counts in blood or skin from uninjured animals (baseline or control group). Overall, there was a significant increase in leukocytes in both peripheral blood and wound tissue (Figure 3). Systemically, the numbers of neutrophils and monocytes were significantly elevated, whereas lymphocyte numbers decreased. Total leukocyte counts were higher in baseline-controlled studies than in studies with separate uninjured controls. There was no significant change in overall eosinophil or thrombocyte counts. The higher standardized mean difference of neutrophils than of total leukocytes might be caused by the decrease in lymphocyte counts. Within the lymphocyte population, only B-cell counts were significantly decreased (Figure 3b).

In burn wound tissue, the numbers of neutrophils, macrophages, and mast cells were increased (Figure 3c). Cell migratory activity, mainly tested by adherence to endothelium or in vitro migration assays, was increased in total leukocytes but not in neutrophils (Figure 3d). Migratory activity of leukocytes was lower in baseline-controlled studies than in studies with separate uninjured controls. Antibacterial function of neutrophils was decreased after burn injury, whereas there was no significant effect on ROS production or inflammatory mediator secretion by neutrophils. The secretion of inflammatory mediators by macrophages was increased.

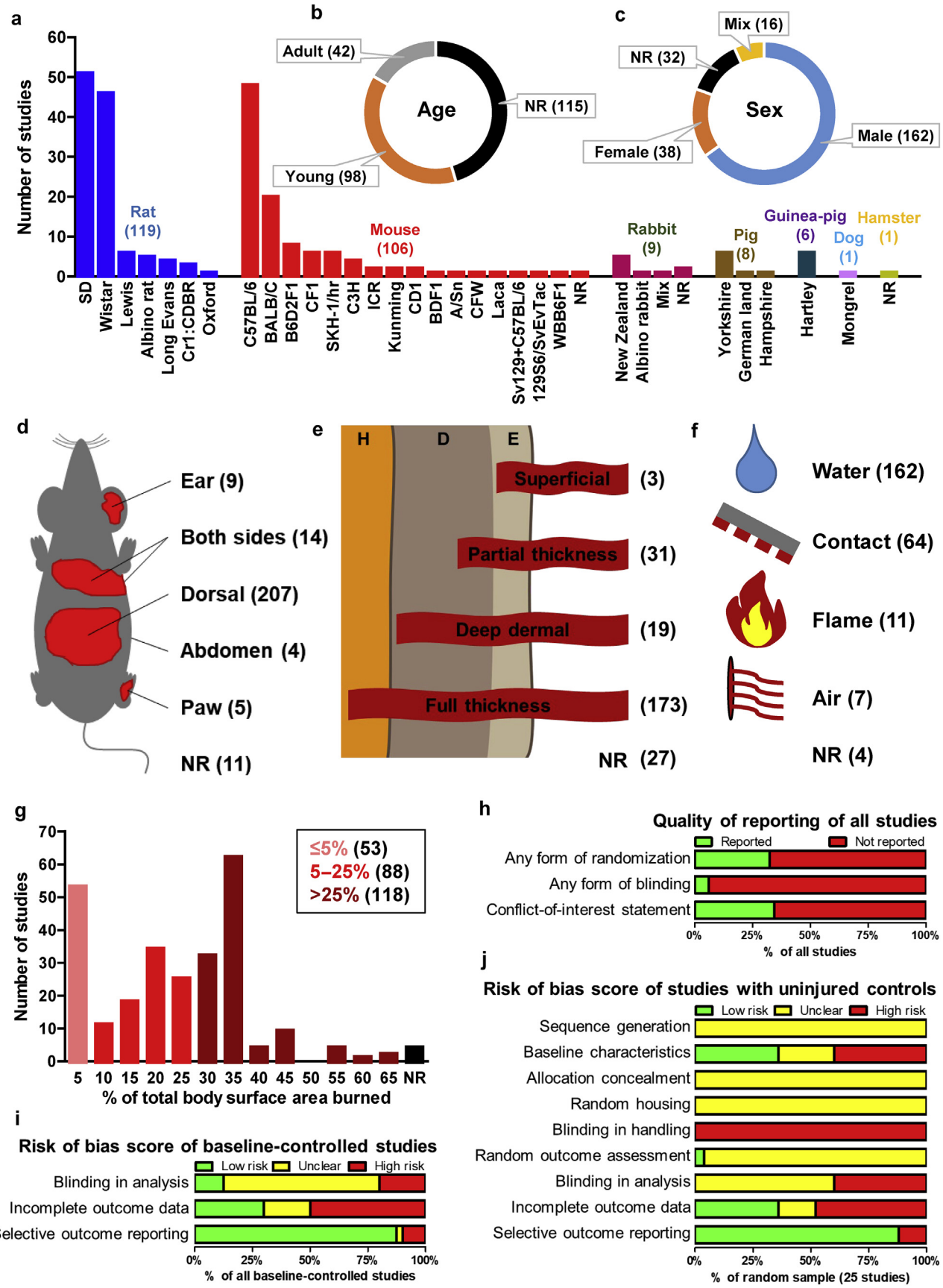


Figure 2. Characteristics of studies in systematic review and risk of bias assessment. Numbers indicate the number of studies. **(a)** Types of animal species and strains. **(b)** Age of study animals. **(c)** Sex of study animals. **(d)** Location of burn injury. **(e)** Depth of burn injury. **(f)** Type of burn agent. **(g)** TBSA that was burned as a percentage. **(h)** Quality of reporting of all included studies. **(i)** Risk of bias assessment of all baseline-controlled studies. **(j)** Complete risk of bias assessment of a random sample consisting of 25 of the included studies. D, dermis; E. Epidermis; H, hypodermis; NR, not reported; TBSA, total body surface area.

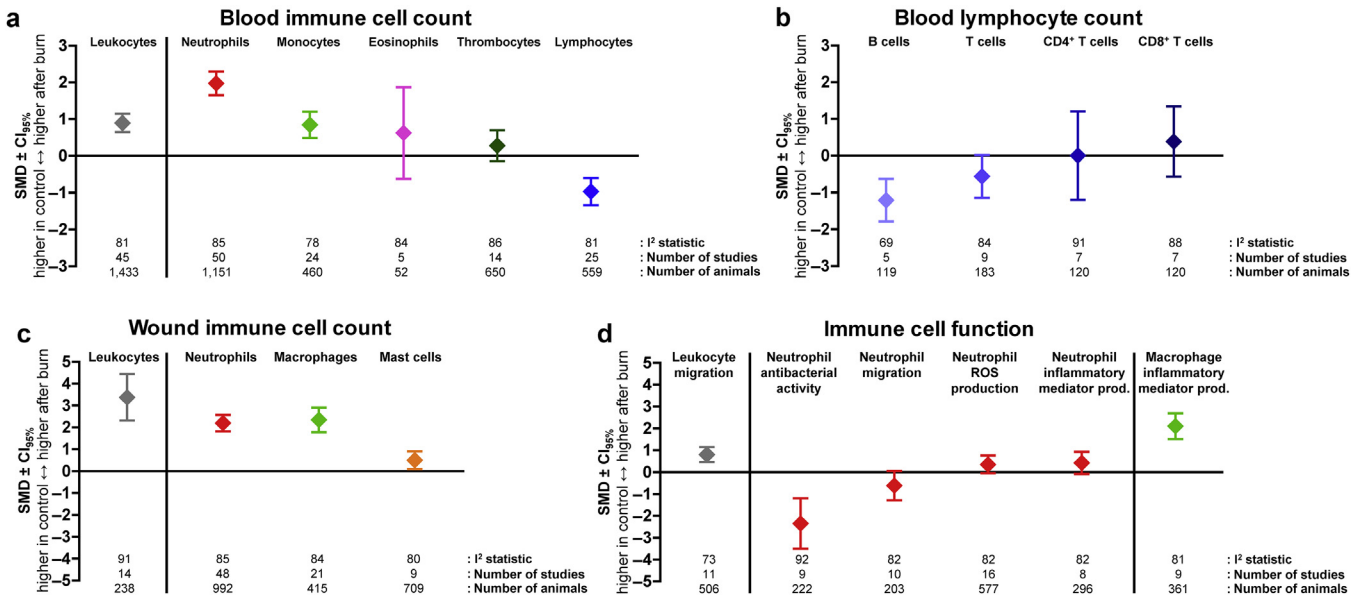


Figure 3. Overall outcome of immune cell counts and function after burn injury. Overall meta-analysis of **(a)** blood immune cell counts, **(b)** blood lymphocyte counts, **(c)** wound immune cell counts, and **(d)** immune cell functions. Results are shown as SMD of immune cell counts in the blood or wound tissue from burn-injured animals compared with immune cell counts in blood or skin from uninjured animals (baseline or control group) ± $CI_{95\%}$. The I^2 statistic, number of studies, and the total number of animals used in the burn group for each meta-analysis are shown below the graphs. $CI_{95\%}$, 95% confidence interval; SMD, standardized mean difference.

There were not enough studies reporting total lymphocyte counts in wound tissue to be included in the meta-analysis.

Blood innate response intensifies and is persistent

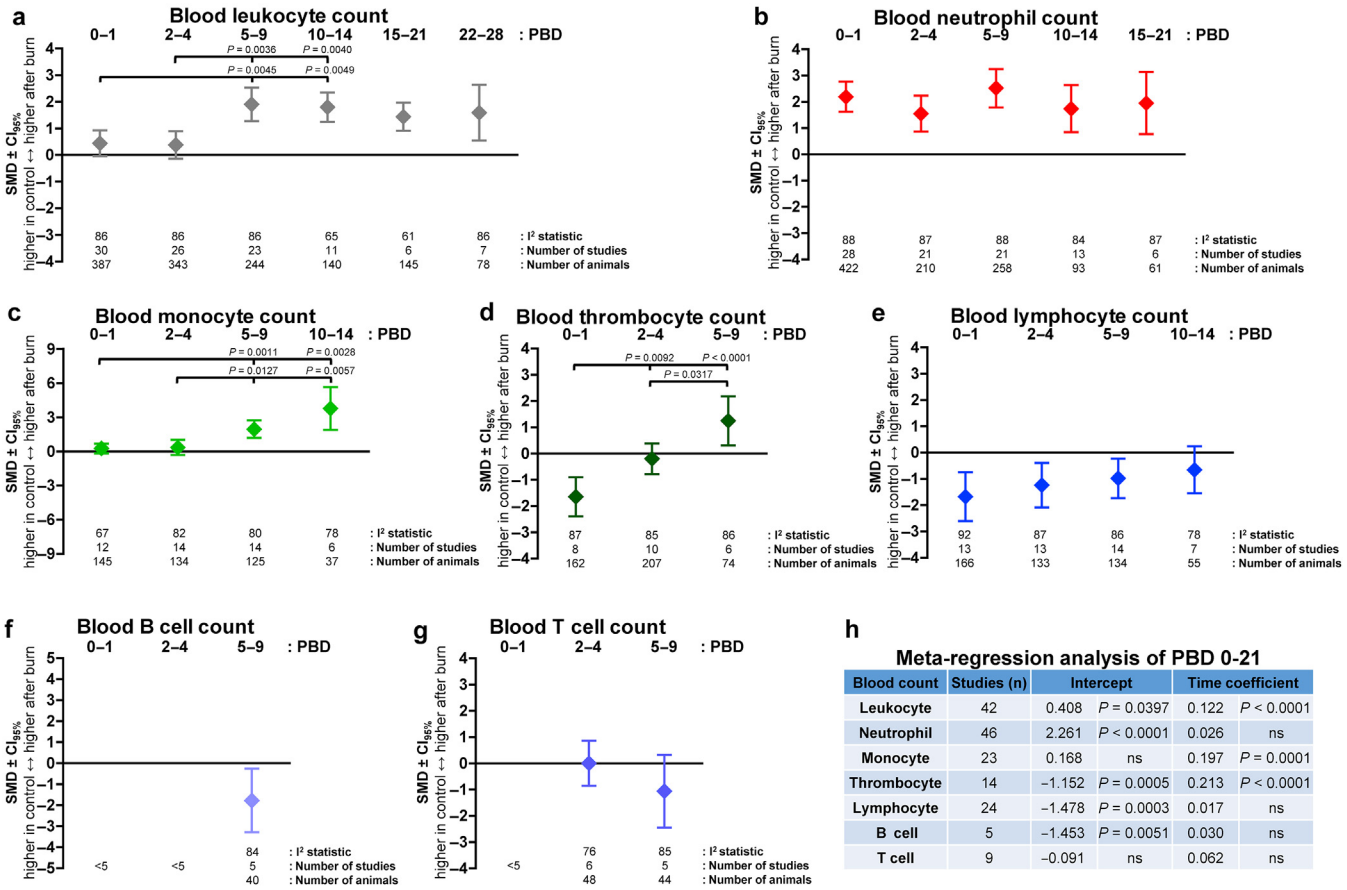
We performed longitudinal analysis on selected time intervals encompassing the four different biological phases of wound healing: hemostasis, inflammation, proliferation, and remodeling (Figure 4a–g). Meta-regression analyses were performed from postburn day (PBD) 0 until PBD 21 (Figure 4h). Blood leukocytes displayed a steady increase, with the highest counts from PBD 5 until PBD 28 (Figure 4a). Neutrophil counts were immediately increased during injury and remained elevated up to PBDs 15–21 (Figure 4b). Monocyte counts were increased from PBD 5 until PBD 14 (Figure 4c). Thrombocyte counts were decreased on PBDs 0–1 and later increased on PBDs 5–9 (Figure 4d). The decline of lymphocytes was most predominant directly after burn injury, whereas on PBDs 10–14, counts returned to control levels (Figure 4e). We detected a decrease in B-cell counts on PBDs 5–9 but found no significant differences in T-cell counts (Figure 4f and g). To further investigate the opposed dynamics of neutrophils and lymphocytes during burn injury, we calculated the neutrophil/lymphocyte ratio (NLR) for studies that reported both neutrophil and lymphocyte counts (Supplementary Figure S1). During the first 9 days, significantly higher NLRs were observed in burn-injured animals, which is an indication of systemic inflammatory response syndrome (Fuss et al., 2018). Overall, the temporal analysis revealed that whereas the increase in neutrophil counts was immediate, total leukocyte, monocyte, and thrombocyte counts increased during the first week, whereas lymphocyte numbers decreased.

Direct innate response in wound is accompanied by altered functions

Longitudinal analyses were performed on cell counts in wound tissue as well as on cell function (Figure 5) and revealed an instant increase in leukocyte migratory activity on PBDs 0–4 and an increase in wound leukocyte numbers on PBDs 0–1 and 5–9 (Figure 5a and b). Mast cell numbers showed a decrease around PBDs 2–4 and a subsequent increase from PBD 10 until PBD 21 (Figure 5c). On the other hand, neutrophil numbers increased instantly and remained elevated until at least PBD 14 (Figure 5d). Although the production of ROS by neutrophils was not significantly altered by burn injury, we did detect an increase in inflammatory mediator secretion by neutrophils on PBDs 0–1 and decreased neutrophil antibacterial activity on PBDs 5–9 (Figure 5e–g). Macrophage numbers increased immediately and remained elevated until PBD 14 (Figure 5h). Release of inflammatory mediators by macrophages was increased on PBDs 0–4 (Figure 5i). Altogether, the instant increase of innate immune cells in wound tissue persisted for at least 2 weeks, whereas certain functions were affected.

Immune response depends on animal characteristics and burn technique

To investigate the differences between experimental models, subgroup analyses were performed (Figure 6). The highest blood leukocyte counts were found in rats or in adult animals. Sensitivity analyses confirmed that the interspecies effect was still present when only young animals were compared and that the difference from aging remained when only rats were analyzed. Neutrophil counts were higher in studies using >25% total body surface area (TBSA) than in those using 5–25% TBSA and were highest in rats. Sensitivity



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Meta-regression analysis of PBD 0-21

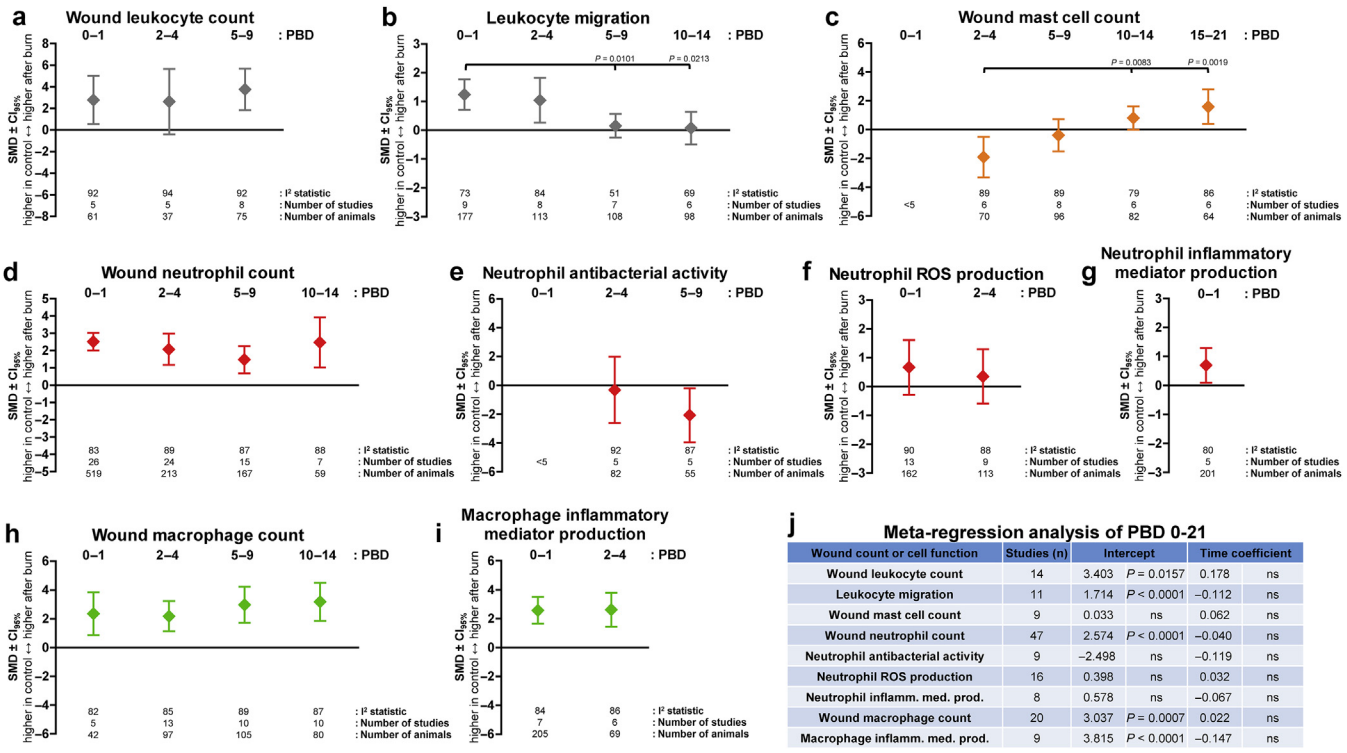
Blood count	Studies (n)	Intercept		Time coefficient	
Leukocyte	42	0.408	$P = 0.0397$	0.122	$P < 0.0001$
Neutrophil	46	2.261	$P < 0.0001$	0.026	ns
Monocyte	23	0.168	ns	0.197	$P = 0.0001$
Thrombocyte	14	−1.152	$P = 0.0005$	0.213	$P < 0.0001$
Lymphocyte	24	−1.478	$P = 0.0003$	0.017	ns
B cell	5	−1.453	$P = 0.0051$	0.030	ns
T cell	9	−0.091	ns	0.062	ns

Figure 4. Longitudinal analyses of blood immune cell counts after burn injury. Longitudinal meta-analysis of blood cell counts: **(a)** leukocytes, **(b)** neutrophils, **(c)** monocytes, **(d)** thrombocytes, **(e)** lymphocytes, **(f)** B cells, and **(g)** T cells. **(h)** Meta-regression with immediate effect (intercept) and linear coefficient of time after burn (PBD 0 until PBD 21). Results are shown as SMD of immune cell counts in blood from burn-injured animals compared with immune cell counts in blood from uninjured animals (baseline or control group) ± $CI_{95\%}$. The I^2 statistic, number of studies, and the total number of animals used in the burn group for each interval are shown below the graphs. Bonferroni-corrected *P*-values of significant differences between time intervals are given in the graphs. $CI_{95\%}$, 95% confidence interval; PBD, postburn day; SMD, standardized mean difference.

analysis showed that the effect of TBSA was present in mice but not in rats. Surprisingly, neutrophil wound counts in studies using 5−25% TBSA were lower than in those using ≤5% TBSA, in both mice and rats. Blood neutrophil counts were higher in males than in females. Interestingly, both wound leukocyte and neutrophil counts were lower in scalds than in metal burns. Within TBSA groups, the difference between species was still present in wound tissue but not in blood, indicating that colinearity could play a role. The difference between sexes for blood counts and the effect of metal burns on wound neutrophil counts were not influenced by TBSA or species. Because the majority of the studies used full-thickness burns, subgroup analysis on wound depth could only be performed for wound neutrophil counts. Overall, the leukocyte response was affected by type of species, animal age, and burn agent, whereas the neutrophil counts depended on species, sex, wound size, and burn agent.

DISCUSSION

An improved understanding of the burn-induced immune response is necessary to prevent secondary pathologies in patients with burns as much as possible. In this study, we synthesized available literature on the postburn immune response in animals into a comprehensive systematic overview. Even though there was great heterogeneity and variation among the studies, the meta-analyses clearly displayed the dynamics of innate and adaptive immune cells after burn injury. In peripheral blood, the numbers of neutrophils, monocytes, and thrombocytes increased shortly or within 1 week after burn injury and remained increased over the first month. In contrast, lymphocyte numbers were reduced during the first 2 weeks, indicating that the response is driven by the innate arm of the immune system and that resolution of inflammation is delayed. In wound tissue, we observed an immediate surge of neutrophils and macrophages during the first 2 weeks, whereas for mast cells, a time-dependent response was observed because numbers decreased near the end of the first week and steadily increased from PBD 10 onward. Although several studies investigated the specific subsets of lymphocytes in wound tissue, there were not enough data available on total lymphocyte counts. Furthermore, burn injury affected cell function because we showed that migration of leukocytes and inflammatory mediator production by neutrophils and macrophages were increased



j Meta-regression analysis of PBD 0-21

Wound count or cell function	Studies (n)	Intercept		Time coefficient	
Wound leukocyte count	14	3.403	$P = 0.0157$	0.178	ns
Leukocyte migration	11	1.714	$P < 0.0001$	−0.112	ns
Wound mast cell count	9	0.033	ns	0.062	ns
Wound neutrophil count	47	2.574	$P < 0.0001$	−0.040	ns
Neutrophil antibacterial activity	9	−2.498	ns	−0.119	ns
Neutrophil ROS production	16	0.398	ns	0.032	ns
Neutrophil inflamm. med. prod.	8	0.578	ns	−0.067	ns
Wound macrophage count	20	3.037	$P = 0.0007$	0.022	ns
Macrophage inflamm. med. prod.	9	3.815	$P < 0.0001$	−0.147	ns

Figure 5. Longitudinal analyses of wound immune cell counts and cell function after burn injury. Longitudinal meta-analysis of **(a)** burn wound leukocyte counts, **(b)** leukocyte migration, **(c)** burn wound mast cell counts, **(d)** burn wound neutrophil counts, **(e)** neutrophil antibacterial activity, **(f)** neutrophil ROS production, **(g)** neutrophil inflammatory mediator production, **(h)** burn wound macrophage counts, and **(i)** macrophage inflammatory mediator production. **(j)** Meta-regression with the immediate effect (intercept) and linear coefficient of time after burn (PBD 0 until PBD 21). Results are shown as SMD of immune cell counts in wound tissue from burn-injured animals compared with immune cell counts in the skin from uninjured animals (baseline or control group) ± $CI_{95\%}$. The I^2 statistic, number of studies, and the total number of animals in the burn group for each interval are shown below the graphs. Bonferroni-corrected *P*-values of significant differences between intervals are given in the graphs. $CI_{95\%}$, 95% confidence interval; inflamm., inflammatory; med., mediator; NS, not significant; PBD, postburn day; prod., production; SMD, standardized mean difference.

earlier on and that antibacterial activity of neutrophils was reduced on PBDs 5–9.

In general, wound healing entails four biological phases, namely hemostasis, inflammation, proliferation, and remodeling. The immediate increase in thrombocyte and neutrophil numbers during the inflammation phase is attenuated within the first week (Rodrigues et al., 2019; Velnar et al., 2009; Zomer and Trentin, 2018). Macrophage numbers, which are important for the transition from inflammation to proliferation (Kotwal and Chien, 2017), normalize later on, whereas lymphocyte numbers increase from the second week onward (Guillamat-Prats, 2021). In this study, we show that at least in animals, these processes are derailed and that high numbers of circulatory thrombocytes, neutrophils, and monocytes are persistent, whereas lymphocyte numbers are actually reduced. This suggests that the timing in typical schematic depictions of the cellular immune response during wound healing does not hold true for burn injury. Unlike in humans, B-cell counts in uninjured rodents are higher than their T-cell counts (Hensel et al., 2019), which could explain the larger effect of burn injury on B cells than on T cells that we found in animals. A relative increase in innate immune cells and a decrease in lymphocytes have also been detected in patients with burns (Laggner et al., 2022; Mulder et al., 2021). Danger-associated molecular patterns that are released by wounded tissues are suggested to cause a continuous activation of the immune system (Comish et al., 2020; Jeschke et al., 2011). In turn, a hyperactive immune system can cause damage to surrounding tissues, thereby producing additional danger-associated molecular patterns and cytokines that uphold the inflammation.

The time-dependent response of thrombocytes is similar to the early thrombocyte response in burn patients (Marck et al., 2013). The typical early trauma-induced leukopenia in patients with burn wounds that is caused by exsanguination, resuscitation, and emigration of immune cells from the blood circulation was in our meta-analysis only visible when the early time points were analyzed per day. Leukopenia is naturally restored by the bone marrow (Osuka et al., 2019; Sen et al., 2019). During acute inflammation, predominantly, neutrophils and monocytes are replenished by the bone marrow, which can lead to reduced lymphopoiesis and overrepresentation of innate immune cells in the circulation (Manz and Boettcher, 2014). Moreover, the NLR, a marker for systemic inflammatory response syndrome in humans, was in animals also highly increased during the first 9 days after burns. In patients with burns, persistent leukocytosis in combination with lymphopenia is associated with persistent inflammation, arrested wound healing, increased susceptibility to opportunistic infection, and increased mortality (Heffernan et al., 2012; Pantalone et al., 2021; Thakkar et al., 2018). Because the

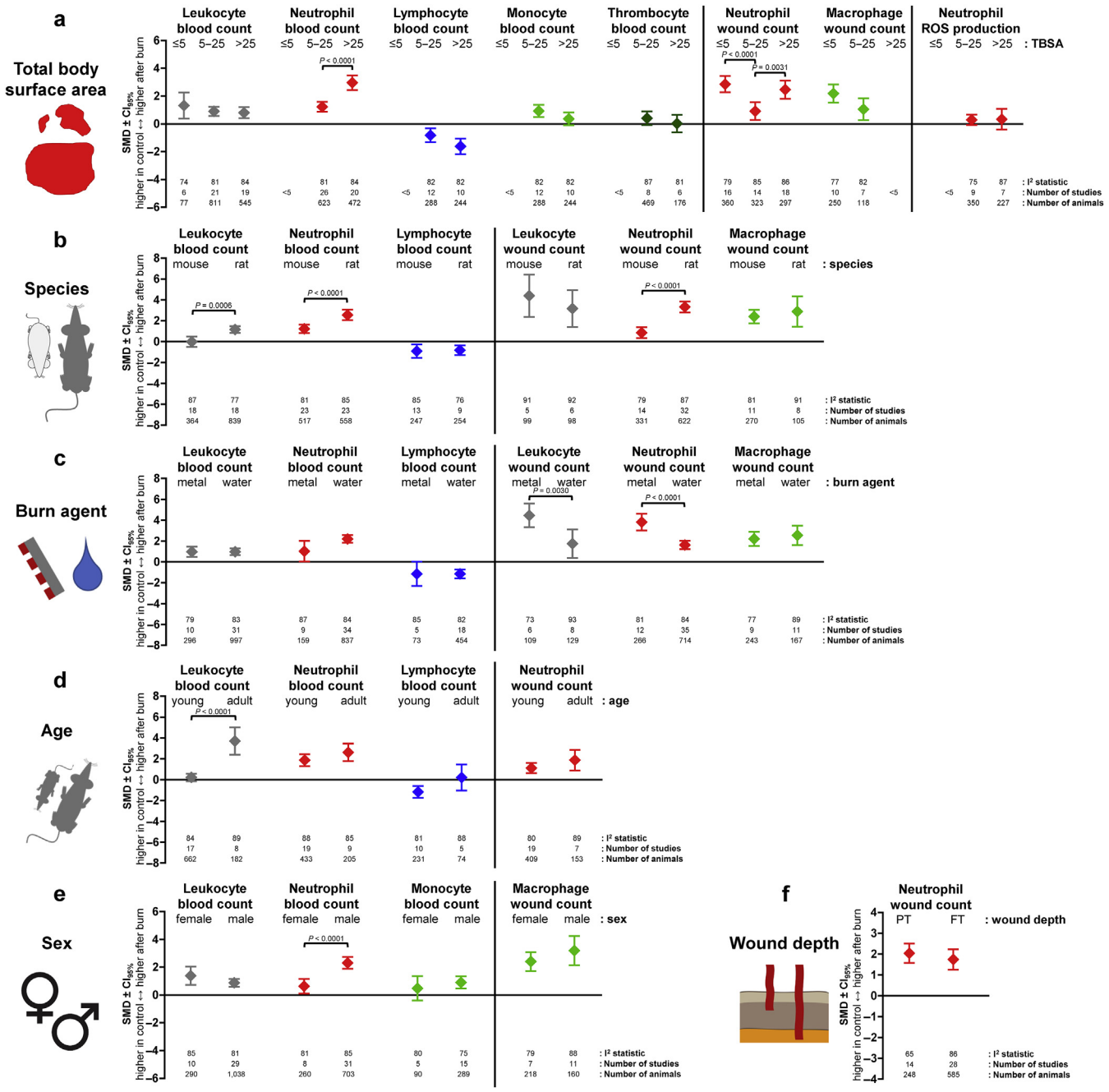


Figure 6. Subgroup analysis of immune cell counts after burn injury. Subgroup analysis of **(a)** burned TBSA, **(b)** species, **(c)** burn agent, **(d)** age, **(e)** sex, and **(f)** wound depth. Only subgroups for which at least five articles were available were used in the analysis. Results are shown as SMD of immune cell counts in blood or wound tissue from burn-injured animals compared with immune cell counts in blood or skin from uninjured animals (baseline or control group) ± $CI_{95\%}$. The I^2 statistic, number of studies, and the total number of animals in the burn group for each subgroup are shown below the graphs. Bonferroni-corrected *P*-values of significant differences between subgroups are given in the graphs. $CI_{95\%}$, 95% confidence interval; FT, full-thickness; PT, partial-thickness; SMD, standardized mean difference; TBSA, total body surface area.

thrombocyte count and NLR correspond with systemic inflammatory response syndrome and septic events, they are of prognostic and diagnostic value (Fuss et al., 2018; Hu et al., 2021).

In wound tissue of animals, increased levels of neutrophils, macrophages, and mast cells were detected until at least PBD 14. The transition of macrophages from an M1 phenotype toward an M2 phenotype is essential to facilitate proper wound healing (Italiani and Boraschi, 2014; Olingy et al., 2017). Although monocyte or macrophage subtypes could not be investigated, we found that total wound macrophage numbers were increased and that the production of inflammatory mediators by macrophages was enhanced. The activity of neutrophils is altered after severe trauma in animals (Baskaran et al., 2000; Janicova et al., 2021; Leliefeld et al., 2016; Mortaz et al., 2018), but it remains unclear whether trauma, in general, enhances or weakens neutrophil activity (Figure 5). Presumably, the emergency release of neutrophils

into the circulation is responsible for reduced chemotactic activity owing to the inflexibility of the banded nucleus of immature neutrophils (Drifte et al., 2013), whereas rapid activation can lead to impaired antibacterial activity (Leliefeld et al., 2016). On the other hand, the immaturity of neutrophils could amplify the granule content and increase the release of inflammatory factors (Manley et al., 2018; Yang et al., 2021). Mast cells have also been proposed to play an active role during wound healing in both animals and humans. They might enhance inflammation and vascular permeability through the secretion of histamines early after injury and stimulate re-epithelization and angiogenesis later on by the release of GFs (Ud-din et al., 2020; Weller et al., 2006). This coincides with increased numbers of mast cells on PBDs 0–1 and on PBDs 15–21.

Only a minority of studies used porcine or canine models, and therefore it was unfeasible to study the differences between species other than mice and rats. Although pigs come close to the human condition in terms of similar skin characteristics and physiology, porcine models are less attractive because of ethical concerns, higher expenses, and advanced operating requirements (Vlig et al., 2019). Subgroup analyses revealed that blood leukocyte and neutrophil counts were more abundant in rats than in mice. Because rats are larger animals, require a longer healing time, and are immunologically more similar to humans than mice (Kim et al., 2015), they might exhibit a more severe immune response than mice. In addition, murine studies generally analyzed the effects shortly after burn injury, thereby causing an overrepresentation of early sampling times. The severity of leukocytosis seemed to increase with animal age and may be explained by the fact that a young, underdeveloped immune system is supposedly tolerant and becomes gradually more active during maturity (Simon et al., 2015). Interestingly, neutrophil responses appeared to depend on burn size and agent. The relationships between the burn size and inflammatory response in humans have been proposed before by others (Barber et al., 2008; Jeschke et al., 2007; Yang et al., 2021). Metal burns induced a greater total leukocyte and neutrophil response in wound tissue than scalds. Water, mostly used at 100 °C, loses heat more rapidly and might therefore cause a less severe injury than metal. It was hardly possible to explore the differences related to wound depth because the majority of studies applied a full-thickness burn wound. Although most studies reported full-thickness injuries, only a limited number of studies actually investigated the wound depth. In addition, wound depth is more prone to subjectivity and depends on many factors such as skin thickness, burn temperature, and duration. Therefore, wound depth was a less useful parameter in these studies.

Numerous studies failed to adhere to the Animal Research: Reporting of In Vivo Experiments guidelines (du Sert et al., 2020) and did not provide important experimental details or information on the number of animals or SDs, which are crucial to performing meta-analyses. The inability to apply blinding might have influenced the data acquisition, and owing to the poor reporting of studies, the general RoB was largely unclear. The improper design, conduct, and reporting in many animal studies have already been described in recent reviews (de Vries et al., 2014; Hooijmans et al., 2014b; Osborne et al., 2018), and future research will surely benefit from more standardized design and reporting (Hao and Nourbakhsh, 2021). Researchers have shown that resuscitation and pain treatment can influence immune reactions after thermal injury (Gómez et al., 2020; Sun et al., 2013). Owing to large variation in the type of anesthetic, resuscitation procedure, and pain management, specific effects on the immune response could not be investigated. Likewise, subgroup analysis of the different methods used to identify cell types was not possible. The overall cell counts showed substantial heterogeneity ($I^2 = 68–92$), which can be expected for animal studies (Hooijmans et al., 2014a). In a few subgroup analyses, a trivial reduction of the I^2 statistic could be detected.

Although animal studies provide valuable insight into the postburn immune response and wound repair, appropriate translation of these findings to the human situation remains crucial to predicting and treating consequential complications effectively. There are several considerable (physiological) differences that make it difficult to convert treatment opportunities directly to patients. Rodents, unlike humans, have more lymphocytes than innate cells, and receptor binding and cytokine responses differ owing to evolution and distinct history of microbial exposure (Mestas and Hughes, 2004; Tao and Reese, 2017). In addition, there are important genomic and evolutionary differences that cause mouse models to poorly reflect certain aspects of human disease (Seok et al., 2013). Furthermore, the ultrahygienic environment of laboratory animals makes the immune system, in general, less tolerant (Sellers et al., 2012; Tao and Reese, 2017). Still, important aspects of the burn-induced human immune response were also present in our meta-analyses, exemplified by the response of thrombocytes, neutrophils, and monocytes (Laggner et al., 2022; Mulder et al., 2021).

Altogether, this review of the burn-induced immune response in animals using meta-analyses puts in perspective the uncontrolled, hyperactive response of immune cells that persists for weeks after burn trauma. Although numerous physiological processes are distinct, many aspects of the human immune response to burns were found in our meta-analyses, including the innate and lymphocyte response and the dynamics of mast cells and thrombocytes. We anticipate that this knowledge will guide the design of future experimental models while supporting the reduction, refinement, and replacement of animal experimentation. It will lead, to our knowledge, to previously unreported insights in clinical research on burn trauma that can ultimately improve burn care and outcome.

MATERIALS AND METHODS

Study protocol and eligibility criteria

A review protocol was established beforehand and is registered at the International Prospective Register of Systematic Reviews (CRD42019136270; http://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=13627). We amended this protocol once to further specify the meta-analyses. The 10-article requirement was changed to five to enable the inclusion of additional cell types.

Search strategy

The search was performed using PubMed and Embase (Leenaars et al., 2012) (Supplementary File S1), with a final update on August 6, 2021. Briefly, we searched for articles with primary data on the immune response in animals with burn injury (search components: burn wound, immune response, and animal). No language or publication date restrictions were applied. Search results were combined, and duplicates were removed using EndNote software (X9, Clarivate Analytics, London, United Kingdom).

Study selection

Studies were selected independently by PPGM and BKHLB using Rayyan (Rayyan Systems, Cambridge, MA) (Ouzzani et al., 2016) in three phases. Discrepancies between the two reviewers were carefully checked, and in case of doubt, references were included. Inaccessible articles were noted (Supplementary File S1) and excluded from the review.

Study characteristics

Independently, PPGM and BKHLB extracted the study characteristics (animal species and strain, age, sex, weight, burn size, burn time, burn agent, burn temperature, burn depth, anatomical location, type of control, cell type, detection method), each from half of the included studies. A random sample of 10% of the extracted data was checked by the other reviewer.

Study quality and RoB assessment

Reporting of any form of randomization or blinding and the presence of a conflict-of-interest statement was scored for all included studies by PPGM and BKHLB who both assessed half of the studies and checked at least 10% of those of the other reviewer. Full RoB assessment was conducted using SYRCLE's tool (Hooijmans et al., 2014b) on 25 randomly selected studies (random number generator; Excel, Microsoft, Redmond, WA). Because only items 7, 8, and 9 from the RoB tool apply to baseline-controlled studies, we evaluated those studies separately. The RoB was evaluated independently by PPGM and BKHLB. In the case of discrepancies, a third reviewer was consulted.

Outcome data extraction

All quantitative outcome measures related to immune cells were collected in a database, which is available on request. PPGM and BKHLB independently extracted the outcome measures (mean outcome and SD, unit of measurement, number of animals), each from half of the included studies, and checked at least 10% of those of the other reviewer.

Synthesis of results and meta-analysis

Meta-analyses were only performed on outcome measures of at least five studies. Data were analyzed using Comprehensive Meta-Analysis (version 3; Biostat, Englewood, NJ), and the effect sizes were expressed as standardized mean difference of immune cell counts in blood or wound tissue from burn-injured animals compared with counts in blood or skin from uninjured animals (baseline or uninjured control) with 95% confidence interval. A random-effects model was used in the analyses, and I^2 statistic was used as a measure for statistical heterogeneity. Cell types that were considered the same entity were pooled (Supplementary Table S1). Possible publication bias was explored using Duval and Tweedie's trim and fill methodology (Supplementary File S2). NLRs were calculated using absolute data from studies that measured both blood neutrophil and lymphocyte counts.

Subgroup analysis and meta-regression

Predefined subgroup analyses were performed. *P*-values were based on the 95% confidence interval of the differences between subgroups. For both longitudinal and subgroup analyses, Bonferroni correction was applied, that is, the *P*-values were multiplied by the number of comparisons made within each subgroup analysis. Differences between baseline-controlled studies and studies with a separate control group were assessed. Meta-regression analyses were performed posthoc on the standardized mean difference of cell counts and cell function using time after burn injury as a continuous variable, including PBD 0 until PBD 21 (Supplementary File S2). Random effects–restricted maximum likelihood model was used, and repeated measures (same animal, multiple sampling times) of studies were included.

See Supplementary Materials and Methods for more detailed information.

Data availability statement

Datasets are available on request after signing a material transfer agreement, please contact pmulder@burns.nl or bboekema@burns.nl.

Studies included in the systematic review

The following references were included in the systeatic review: Abali et al., 2015; Abbas et al., 2018, 2017; Abd et al., 2020; Abdallah Hajj Hussein et al., 2012; Abo El-Noor et al., 2017; Adediran et al., 2010; Akgun et al., 2017; Akhzari et al., 2017; Alexander et al., 2006; Alexis et al., 2015; Alyoussef et al., 2021; Asko Seljavaara, 1974; Avsar et al., 2016; Babcock et al., 2012; Bankova et al., 2014; Baskaran et al., 2000; Bayat et al., 2008; Bayliss et al., 2014; Beckmann et al., 2021; Begieneman et al., 2012; Bird et al., 2010; Bjornson et al., 1992, Bjornson et al., 1989, Bjornson et al., 1988, 1986; Bohannon et al., 2008; Bohr et al., 2013a, 2013b; Brandenburg et al., 2019a, Brandenburg et al., 2019b; Brownstein et al., 2006; Burleson et al., 1988, Burleson et al., 1987; Burmeister et al., 2016; Cakir et al., 2005; Calum et al., 2009; Chakraborty et al., 2018; Chao et al., 2020; D'Alesandro and Gruber, 1990; Daniel et al., 2007; de David Antoniazzi et al., 2018; Davis and Gallin, 1988; Deitch et al., 2006; Dinescu et al., 2019; Dokumcu et al., 2008; Dong et al., 2015, Dong et al., 1993a, Dong et al., 1993b; Duansak et al., 2003; Duque et al., 1985; Eski et al., 2001; Eurenius and Brouse, 1973; Fan et al., 2016; Fang et al., 2017; Faunce et al., 2003, Faunce et al., 1999; Fazal et al., 2012, Fazal et al., 2001, Fazal et al., 1997; Fear et al., 2016; Fiório et al., 2014; Fried et al., 1991; Fuchs et al., 2006; Fujimi et al., 2006; Gadd and Hansbrough, 1989; Gamelli et al., 1985; Gao et al., 2019; Gardner et al., 2014; Goertz et al., 2016, Goertz et al., 2012, 2011, Goertz et al., 2009; Gómez et al., 2020, Gómez et al., 2018; Goto et al., 2006; Groger et al., 2010; Gruber and D'Alesandro, 1989; Gruber and Farese, 1989; Guo et al., 2015; Guo and Gu, 1988; Hansbrough et al., 1996a, Hansbrough et al., 1996b, 1996c, 1987; Hansbrough and Gadd, 1989; He et al., 2001; Heideman, 1979; Heinrich et al., 2003; Hemmila et al., 2010; Hernekamp et al., 2012; Higashimori et al., 2006; Howell et al., 2012; Hu and Sayeed, 2005, 2004; Hummel et al., 1966; Ibrahim et al., 2014; Ikeuchi et al., 1981; Inoue et al., 2018; Ipaktchi et al., 2007, 2006; Iwashita et al., 1999; Jabeen et al., 2019; Jahovic et al., 2004; Jian-Xing et al., 2021; Jiao et al., 2020; Jin et al., 2017; Johnson et al., 2016; Jurjus et al., 2018, 2007; Kabasakal et al., 2005; Katakura et al., 2004; Khalid et al., 2019; Kimura et al., 2008; Korkmaz et al., 2020, 2017; Kurihara et al., 2013; Kuroiwa

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CONFLICT OF INTEREST
The authors state no conflicting interest.

ACKNOWLEDGMENTS
We want to thank Alice Tillema of the Radboud University Medical Center Library for helping to design the search strategy; Carlijn Hooijmans of SYstematic Review *Centre* for Laboratory animal Experimentation for her assistance with the data analysis; and Anouk Elgersma, Rosa Rentenaar, and Myrthe Witbaard of the Association of Dutch Burn Centres for their assistance during data extraction. This research is funded by ZonMw More Knowledge with Less Animals under grant 114024139 (PPGM) and the Dutch Burn Foundation under grant WO/17.108 (BKHLB).

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Conceptualization: PPGM, BKHLB, HJPMK, IJ, MV; Formal Analysis: PPGM, BKHLB, RBMDV; Investigation: PPGM, BKHLB; Methodology: PPGM, BKHLB, RBMDV; Supervision: BKHLB, HJPMK, IJ; Visualization: PPGM, BKHLB; Writing — Original Draft Preparation: PPGM, BKHLB; Writing — Review and Editing: HJPMK, IJ, RBMDV, MV

SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2022.05.004

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SUPPLEMENTARY MATERIALS AND METHODS

Study selection

Studies were selected independently by PPGM and BKHLB using Rayyan software (Rayyan Systems, Cambridge, MA) (Ouzzani et al., 2016)) in three phases: title screening, abstract screening, and full-text screening. In the title screening, clearly irrelevant articles (not about burn injury) were excluded. During the abstract screening, studies involving animal skin burns that contained primary data were selected, and reviews, posters, and conference abstracts were excluded. In the full-text screening, we selected articles involving animal thermal burns with outcome measures related to immune cells and without cointerventions that interfere with the function of the immune system, such as infection or anti-inflammatory medication. In addition, the presence of an appropriate control group (either healthy animals, baseline measures, or sham controls) was verified. Discrepancies between the two reviewers were carefully checked, and in case of doubt, references were included. Inaccessible articles were noted (Supplementary File S2) and excluded from the review.

Study quality and risk of bias assessment

The reporting of any form of randomization or blinding and the presence of a conflict-of-interest statement was scored for all included studies by PPGM and BKHLB who both assessed half of the studies and checked at least 10% of those of the other reviewer. Full risk of bias (RoB) assessment was conducted using SYRCLE's tool (Hooijmans et al., 2014) on 25 randomly selected studies (random number generator in Excel, Microsoft, Redmond, WA). We evaluated the reporting of the following baseline characteristics: animal sex, age, or weight (reporting of a range <10% was considered as low RoB). To check the completeness of outcome reporting, we evaluated the number of animals in the method and results section for each experiment and outcome. The RoB was evaluated independently by PPGM and BKHLB. In the case of discrepancies, a third reviewer was consulted. This assessment provided an indication of the RoB of all included studies. Because only items 7, 8, and 9 from the RoB tool apply to baseline controlled studies, we evaluated those studies separately.

Outcome data extraction

All quantitative outcome measures related to immune cells, such as immune cell counts and cell function, were collected in a database, which is available on request. PPGM and BKHLB independently extracted the outcome measures (mean outcome and SD, unit of measurement, number of animals), each from half of the included studies, and checked at least 10% of those of the other reviewer. The following outcome measures in either blood or wound tissue were included: immune cell counts, immune cell migration assays, antibacterial activity, production of inflammatory mediators or ROS by specific cell types, and apoptosis. Data from graphs were extracted using the digital ruler feature in ImageJ (version 1.53j, National Institutes of Health, Bethesda, MD) (Schneider et al., 2012). In case of missing data, such as the number of animals or SD, we contacted corresponding authors by email and ResearchGate (including a reminder after 2 weeks) (response rate = 17%). Data presented as SEM were transformed to SD with the following formula: $SD = SEM \times \sqrt{\text{number of animals}}$.

Subgroup analysis

Predefined subgroup analyses were performed on time after burn (divided into categories 0–1, 2–4, 5–9, 10–14, 15–21, 22–28, or >29 days), burned total body surface area (≤5, 5–25, or >25%), wound depth (superficial, partial thickness, deep dermal, or full-thickness), burn agent (flame, water, or metal), animal species (mouse, rat, or pig), sex, and age (young or adult). In the case of repeated measures within a time interval, the maximum effect size per time interval was chosen. When required, total body surface area was calculated using the reported area of the burn, weight (W) of the animals, and Meeh-Rubner's formula (total body surface area $= \frac{\text{area of burn}}{K * W^{2/3}}$) (Gouma et al., 2012). The following K values were used: 9 (mouse), 9.83 (rat), 12 (rabbit), 10.5 (guinea pig), 10.1 (dog), and 10 (pig). When total body surface area was missing in the articles, it was estimated on the basis of the reported age and weight information available at Animal Resources Centre (https://www.arc.wa.gov.au/), The Jackson Laboratory (https://www.jax.org/), and Roysfarm (https://www.roysfarm.com/). Using the weight of the animal, the animal's age was estimated when this was not reported. Animal age subgroups, young or adult, were based on the social maturity of the animals: adults were aged >3 months (mouse), >6 months (rat), >6 months (pig), >12 weeks (hamster), >12 months (rabbit), >6 months (Guinea pig), and >1 year (dog). For wound depth, the following categories were used: superficial (first degree), partial thickness (second degree), deep dermal (deep second degree), and full thickness (third degree, fourth degree, severe burn injury). *P*-values were based on the 95% confidence interval of the difference between subgroups. For both longitudinal and subgroup analyses, Bonferroni correction was applied, that is, the *P*-values were multiplied by the number of comparisons within each subgroup analysis. Differences between baseline controlled studies and studies that used a separate control group were assessed.

Baseline-controlled studies that were used for RoB assessment

The baseline-controlled studies used for RoB assessment include the following: Abdallah Hajj Hussein et al., 2012; Abo El-Noor et al., 2017; Begieneman et al., 2012; Bohannon et al., 2008; Bohr et al., 2013a, Bohr et al., 2013b; Chakraborty et al., 2018; Chao et al., 2020; D'Alesandro and Gruber, 1990; Fuchs et al., 2006; Goertz et al., 2016, 2012, 2011, 2009; Gómez et al., 2020, 2018; Groger et al., 2010; Heideman, 1979; Hummel et al., 1966; Inoue et al., 2018; Iwashita et al., 1999; Jabeen et al., 2019; Jurjus et al., 2007; Kimura et al., 2008; Langer et al., 2005; Lavaud et al., 1988; Mikhal'chik et al., 2004; Nassar et al., 2012; Nwariaku et al., 1995; Ny et al., 2020; Piccolo et al., 1999; Rawlingson et al., 2003, 2001; Santos et al., 2000; Schwacha et al., 2019; Tian et al., 2016; Till et al., 1983; Yao et al., 1997; and Zhuravleva et al., 2020.

Studies with uninjured controls that were used for RoB assessment

Studies with uninjured controls that were used for RoB assessment included the following: Abbas et al., 2018, 2017; Asko Seljavaara, 1974; Dong et al., 1993a; Duque et al., 1985; Eurenius and Brouse, 1973; Fazal et al., 2012, 1997; Gardner et al., 2014; Hansbrough et al., 1987; Hernekamp et al., 2012; Madihally et al., 2001; Maung et al., 2008; Miles et al., 1999; Nishikori et al., 1998; Noel et al., 2010; Pallua et al., 2003; Schindel et al., 1997; Shallo et al., 2003; Sheeran et al., 1998; Souza et al., 2017; Wang et al., 2002; Xiao et al., 2016, 2013; and Yang et al., 2013a.

SUPPLEMENTARY FILE S1: SEARCH STRATEGY, SEARCH RESULTS, AND INACCESSIBLE REFERENCES

Search strategy PubMed (Medline)

Search component 1. This includes burns[MeSH] OR burns [tiab] OR burn[tiab] OR burnt[tiab] OR burned[tiab] OR scald[tiab] OR scalds[tiab] OR thermal injur*[tiab] OR thermal wound*[tiab] OR heat injur*[tiab] OR heat wound*[tiab]

Search component 2. This includes cytokines[MeSH] OR Inflammation mediators[MeSH] OR Immunoproteins[MeSH] OR Complement System Proteins[MeSH] OR EGF Family of Proteins[MeSH] OR Angiogenic Proteins[MeSH] OR Endothelial Growth Factors[MeSH] OR Endothelins[MeSH] OR Kinins[MeSH] OR Platelet-Derived Growth Factor[MeSH] OR TGF-beta Superfamily Proteins[MeSH] OR Transforming Growth Factors[MeSH] OR germinal center*[tiab] OR immune[tiab] OR immunological[tiab] OR immunologic[tiab] OR inflammatory[tiab] OR inflammation[tiab] OR mediators [tiab] OR lymph[tiab] OR lymphatic[tiab] OR lymphoid[tiab] OR accessory cell[tiab] OR B cell*[tiab] OR Bcell*[tiab] OR Blymphocyt*[tiab] OR plasma cell*[tiab] OR basophil*[tiab] OR blood cell*[tiab] OR bone marrow[tiab] OR cardiotrophin*[tiab] OR dendritic cell*[tiab] OR eosinophil*[tiab] OR fibroblast*[tiab] OR myofibroblast*[tiab] OR granulocyt* [tiab] OR langerhans cell*[tiab] OR leukocyt*[tiab] OR leucocyt*[tiab] OR lymphocyt*[tiab] OR megakaryocyt*[tiab] OR macrophag*[tiab] OR foam cell*[tiab] OR histiocyt*[tiab] OR mast cell*[tiab] OR monocyt*[tiab] OR neutrophil*[tiab] OR natural killer*[tiab] OR phagocyt*[tiab] OR cytophagocyt*[tiab] OR plasmablast*[tiab] OR stem cell*[tiab] OR T cell*[tiab] OR Tcell*[tiab] OR Tlymphocyt*[tiab] OR Thelp* [tiab] OR activin*[tiab] OR angiotensin[tiab] OR anaphylatox*[tiab] OR arachidon*[tiab] OR autotoxin*[tiab] OR chemokine*[tiab] OR cluster of differentiat*[tiab] OR cytokine* [tiab] OR ectodysplasin*[tiab] OR growth factor*[tiab] OR growth differentiation[tiab] OR TGF*[tiab] OR helper factor* [tiab] OR interferon*[tiab] OR IFN*[tiab] OR interleukin* [tiab] OR kinin*[tiab] OR lymphokine[tiab] OR lymphokines [tiab] OR lymphotoxin[tiab] OR lymphotoxins[tiab] OR lymphopoietin[tiab] OR lymphopoietins[tiab] OR migration factor*[tiab] OR migratory factor*[tiab] OR monokin[tiab] OR monokins[tiab] OR myostatin[tiab] OR myostatins[tiab] OR necrosis factor*[tiab] OR necrotic factor*[tiab] OR CCR* [tiab] OR CCL*[tiab] OR CXCL*[tiab] OR CXCR*[tiab] OR CX3C*[tiab] OR lymphotactin*[tiab] OR CRP[tiab] OR c-reactive protein[tiab] OR c reactive protein[tiab] OR histamin*[tiab] OR prostaglandin*[tiab] OR PGE*[tiab] OR alkaline phosphatase*[tiab] OR ALP[tiab] OR ALKP[tiab] OR ALPase[tiab] OR Alk Phos[tiab] OR basic phosphatase[tiab] OR GM-CSF[tiab] OR M-CSF[tiab] OR G-CSF[tiab] OR complement*[tiab] OR membrane attack complex[tiab] OR MAC complex[tiab] OR lectin pathway[tiab] OR alternative pathway[tiab] OR classical pathway[tiab] OR opsoniz*[tiab] OR malondialdehyd*[tiab] OR HMGB1[tiab] OR TSG6[tiab] OR LTB4[tiab] OR MCP*[tiab] OR MIP*[tiab] OR RANTES [tiab] OR CTACK[tiab] OR IP10[tiab] OR GROα[tiab] OR GROa[tiab] OR TNF-α[tiab] OR TNF-β[tiab] OR TNFα[tiab] OR TNFa[tiab] OR TNF-a[tiab] OR TNFb[tiab] OR TNF-b [tiab] OR TNFβ[tiab] OR tumor necrosis factor[tiab] OR IL-1[tiab] OR IL1[tiab] OR IL-1α[tiab] OR IL1α[tiab] OR IL1a [tiab] OR IL1-a[tiab] OR IL-1β[tiab] OR IL1β[tiab] OR IL1b [tiab] OR IL-1b[tiab] OR IL-10*[tiab] OR IL10*[tiab] OR IL-11*[tiab] OR IL-11*[tiab] OR IL-12*[tiab] OR IL12*[tiab] OR IL-13*[tiab] OR IL13*[tiab] OR IL-14*[tiab] OR IL14*[tiab] OR IL-15*[tiab] OR IL15*[tiab] OR IL-16*[tiab] OR IL16* [tiab] OR IL-17*[tiab] OR IL17*[tiab] OR IL-18*[tiab] OR IL18*[tiab] OR IL-19*[tiab] OR IL19*[tiab] OR IL-2*[tiab] OR IL2*[tiab] OR IL-3*[tiab] OR IL3*[tiab] OR IL-4*[tiab] OR IL4*[tiab] OR IL-5*[tiab] OR IL5*[tiab] OR IL-6*[tiab] OR IL6*[tiab] OR IL-7*[tiab] OR IL7*[tiab] OR IL-8*[tiab] OR IL8*[tiab] OR IL-9*[tiab] OR IL9*[tiab] OR Platelet-derived growth factor*[tiab] OR PDGF*[tiab] OR VEGF*[tiab] OR CTLA*[tiab] OR NF-HEV[tiab]

Search component 3. This includes "animal experimentation"[MeSH Terms] OR "models, animal"[MeSH Terms] OR "invertebrates"[MeSH Terms] OR "Animals"[Mesh:noexp] OR "animal population groups"[MeSH Terms] OR "chordata"[MeSH Terms:noexp] OR "chordata, nonvertebrate"[MeSH Terms] OR "vertebrates"[MeSH Terms:noexp] OR "amphibians"[MeSH Terms] OR "birds"[MeSH Terms] OR "fishes"[MeSH Terms] OR "reptiles"[MeSH Terms] OR "mammals"[MeSH Terms:noexp] OR "primates"[MeSH Terms:noexp] OR "artiodactyla"[MeSH Terms] OR "carnivora"[MeSH Terms] OR "cetacea"[MeSH Terms] OR "chiroptera"[MeSH Terms] OR "elephants"[MeSH Terms] OR "hyraxes"[MeSH Terms] OR "insectivora"[MeSH Terms] OR "lagomorpha"[MeSH Terms] OR "marsupialia"[MeSH Terms] OR "monotremata"[MeSH Terms] OR "perissodactyla"[MeSH Terms] OR "rodentia"[MeSH Terms] OR "scandentia"[MeSH Terms] OR "sirenia"[MeSH Terms] OR "xenarthra"[MeSH Terms] OR "haplorhini"[MeSH Terms:noexp] OR "strepsirhini"[MeSH Terms] OR "platyrrhini"[MeSH Terms] OR "tarsii"[MeSH Terms] OR "catarrhini"[MeSH Terms:noexp] OR "cercopithecidae"[MeSH Terms] OR "hylobatidae"[MeSH Terms] OR "hominidae"[MeSH Terms:noexp] OR "gorilla gorilla"[MeSH Terms] OR "pan paniscus"[MeSH Terms] OR "pan troglodytes"[MeSH Terms] OR "pongo pygmaeus"[MeSH Terms]) OR ((animals[tiab] OR animal[tiab] OR mice[Tiab] OR mus[Tiab] OR mouse[Tiab] OR murine[Tiab] OR woodmouse[tiab] OR rats[Tiab] OR rat[Tiab] OR murinae[Tiab] OR muridae[Tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[Tiab] OR rodent[Tiab] OR rodents[Tiab] OR pigs[Tiab] OR pig[Tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus

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[Tiab] OR capybara[Tiab] OR capybaras[Tiab]) NOT medline [sb].

Search strategy PubMed (Medline) EMBASE

Search component 1. This includes exp burn/ OR burns.ti,ab,kw. OR burn.ti,ab,kw. OR burnt.ti,ab,kw. OR burned.ti,ab,kw. OR scald.ti,ab,kw. OR scalds.ti,ab,kw. OR thermal-injur*.ti,ab,kw. OR thermal-wound*.ti,ab,kw. OR heat-injur*.ti,ab,kw. OR heat-wound*.ti,ab,kw.

Search component 2. This includes exp inflammation/ OR exp cytokine/ OR exp peptides and proteins/ OR exp complement/ OR germinal center*.ti,ab,kw. OR immune.ti,ab,kw. OR immunological.ti,ab,kw. OR immunologic.ti,ab,kw. OR inflammatory.ti,ab,kw. OR inflammation.ti,ab,kw. OR mediators.ti,ab,kw. OR lymph.ti,ab,kw. OR lymphatic.ti,ab,kw. OR lymphoid.ti,ab,kw. OR accessory cell.ti,ab,kw. OR B cell*.ti,ab,kw. OR Bcell*.ti,ab,kw. OR Blymphocyt*.ti,ab,kw. OR plasma cell*.ti,ab,kw. OR basophil*.ti,ab,kw. OR blood cell*.ti,ab,kw. OR bone marrow.ti,ab,kw. OR cardiotrophin*.ti,ab,kw. OR dendritic cell*.ti,ab,kw. OR eosinophil*.ti,ab,kw. OR fibroblast*.ti,ab,kw. OR myofibroblast*.ti,ab,kw. OR granulocyt*.ti,ab,kw. OR langerhans cell*.ti,ab,kw. OR leukocyt*.ti,ab,kw. OR leucocyt*.ti,ab,kw. OR lymphocyt*.ti,ab,kw. OR megakaryocyt*.ti,ab,kw. OR macrophag*.ti,ab,kw. OR foam cell*.ti,ab,kw. OR histiocyt*.ti,ab,kw. OR mast cell*.ti,ab,kw. OR monocyt*.ti,ab,kw. OR neutrophil*.ti,ab,kw. OR natural killer*.ti,ab,kw. OR phagocyt*.ti,ab,kw. OR cytophagocyt*.ti,ab,kw. OR plasmablast*.ti,ab,kw. OR stem cell*.ti,ab,kw. OR T cell*.ti,ab,kw. OR Tcell*.ti,ab,kw. OR Tlymphocyt*.ti,ab,kw. OR Thelp*.ti,ab,kw. OR activin*.ti,ab,kw. OR angiotensin.ti,ab,kw. OR anaphylatox*.ti,ab,kw. OR arachidon*.ti,ab,kw. OR autotoxin*.ti,ab,kw. OR chemokine*.ti,ab,kw. OR cluster of differentiat*.ti,ab,kw. OR cytokine*.ti,ab,kw. OR ectodysplasin*.ti,ab,kw. OR

efavaleukin*.ti,ab,kw. OR efineptakin*.ti,ab,kw. OR growth factor*.ti,ab,kw. OR growth differentiation.ti,ab,kw. OR TGF*.ti,ab,kw. OR helper factor*.ti,ab,kw. OR interferon*.ti,ab,kw. OR IFN*.ti,ab,kw. OR interleukin*.ti,ab,kw. OR kinin*.ti,ab,kw. OR lymphokine.ti,ab,kw. OR lymphokines.ti,ab,kw. OR lymphotoxin.ti,ab,kw. OR lymphotoxins.ti,ab,kw. OR lymphopoietin.ti,ab,kw. OR lymphopoietins.ti,ab,kw. OR migration factor*.ti,ab,kw. OR migratory factor*.ti,ab,kw. OR monokin.ti,ab,kw. OR monokins.ti,ab,kw. OR myostatin.ti,ab,kw. OR myostatins.ti,ab,kw. OR necrosis factor*.ti,ab,kw. OR necrotic factor*.ti,ab,kw. OR CCR*.ti,ab,kw. OR CCL*.ti,ab,kw. OR CXCL*.ti,ab,kw. OR CXCR*.ti,ab,kw. OR CX3C*.ti,ab,kw. OR lymphotactin*.ti,ab,kw. OR CRP.ti,ab,kw. OR c-reactive protein.ti,ab,kw. OR c reactive protein.ti,ab,kw. OR histamin*.ti,ab,kw. OR prostaglandin*.ti,ab,kw. OR PGE*.ti,ab,kw. OR alkaline phosphatase*.ti,ab,kw. OR ALP.ti,ab,kw. OR ALKP.ti,ab,kw. OR ALPase.ti,ab,kw. OR Alk Phos.ti,ab,kw. OR basic phosphatase.ti,ab,kw. OR GM-CSF.ti,ab,kw. OR M-CSF.ti,ab,kw. OR G-CSF.ti,ab,kw. OR complement*.ti,ab,kw. OR membrane attack complex.ti,ab,kw. OR MAC complex.ti,ab,kw. OR lectin pathway.ti,ab,kw. OR alternative pathway.ti,ab,kw. OR classical pathway.ti,ab,kw. OR opsoniz*.ti,ab,kw. OR malondialdehyd*.ti,ab,kw. OR HMGB1.ti,ab,kw. OR TSG6.ti,ab,kw. OR LTB4.ti,ab,kw. OR MCP*.ti,ab,kw. OR MIP*.ti,ab,kw. OR RANTES.ti,ab,kw. OR CTACK.ti,ab,kw. OR IP10.ti,ab,kw. OR GROa.ti,ab,kw. OR TNFa.ti,ab,kw. OR TNF-a.ti,ab,kw. OR TNFb.ti,ab,kw. OR TNF-b.ti,ab,kw. OR tumor necrosis factor.ti,ab,kw. OR IL-1.ti,ab,kw. OR IL1.ti,ab,kw. OR IL1a.ti,ab,kw. OR IL1-a.ti,ab,kw. OR IL1b.ti,ab,kw. OR IL-1b.ti,ab,kw. OR IL-10*.ti,ab,kw. OR IL10*.ti,ab,kw. OR IL-11*.ti,ab,kw. OR IL-11*.ti,ab,kw. OR IL-12*.ti,ab,kw. OR IL12*.ti,ab,kw. OR IL-13*.ti,ab,kw. OR IL13*.ti,ab,kw. OR IL-14*.ti,ab,kw. OR IL14*.ti,ab,kw. OR IL-15*.ti,ab,kw. OR IL15*.ti,ab,kw. OR IL-16*.ti,ab,kw. OR IL16*.ti,ab,kw. OR IL-17*.ti,ab,kw. OR IL17*.ti,ab,kw. OR IL-18*.ti,ab,kw. OR IL18*.ti,ab,kw. OR IL-19*.ti,ab,kw. OR IL19*.ti,ab,kw. OR IL-2*.ti,ab,kw. OR IL2*.ti,ab,kw. OR IL-3*.ti,ab,kw. OR IL3*.ti,ab,kw. OR IL-4*.ti,ab,kw. OR IL4*.ti,ab,kw. OR IL-5*.ti,ab,kw. OR IL5*.ti,ab,kw. OR IL-6*.ti,ab,kw. OR IL6*.ti,ab,kw. OR IL-7*.ti,ab,kw. OR IL7*.ti,ab,kw. OR IL-8*.ti,ab,kw. OR IL8*.ti,ab,kw. OR IL-9*.ti,ab,kw. OR IL9*.ti,ab,kw. OR Platelet-derived growth factor*.ti,ab,kw. OR PDGF*.ti,ab,kw. OR VEGF*.ti,ab,kw. OR CTLA*.ti,ab,kw. OR NF-HEV.ti,ab,kw.

Search component 3. This includes exp animal experiment/ or exp animal model/ or exp experimental animal/ or exp transgenic animal/ or exp male animal/ or exp female animal/ or exp juvenile animal/ OR animal/ OR chordata/ OR vertebrate/ OR tetrapod/ OR exp fish/ OR amniote/ OR exp amphibia/ OR mammal/ OR exp reptile/ OR exp sauropsid/ OR therian/OR exp monotremate/ OR placental mammals/ OR exp marsupial/ OR Euarchontoglires/ OR exp Afrotheria/ OR exp Boreoeutheria/ OR exp Laurasiatheria/ OR exp Xenarthra/ OR primate/ OR exp Dermoptera/ OR exp Glires/ OR exp Scandentia/ OR Haplorhini/ OR exp prosimian/ OR simian/ OR exp tarsiiform/ OR Catarrhini/ OR exp Platyrrhini/ OR ape/ OR exp Cercopithecidae/ OR hominid/ OR exp hylobatidae/ OR exp chimpanzee/ OR exp gorilla/ OR exp orang utan/ OR (animal OR animals OR pisces OR fish OR fishes OR catfish OR catfishes OR sheatfish OR silurus OR arius OR heteropneustes OR clarias OR gariepinus OR fathead minnow OR fathead minnows OR pimephales OR promelas OR cichlidae OR trout OR trouts OR char OR chars OR salvelinus OR salmo OR oncorhynchus OR guppy OR guppies OR millionfish OR poecilia OR goldfish OR goldfishes OR carassius OR auratus OR mullet OR mullets OR mugil OR curema OR shark OR sharks OR cod OR cods OR gadus OR morhua OR carp OR carps OR cyprinus OR carpio OR killifish OR eel OR eels OR anguilla OR zander OR sander OR lucioperca OR stizostedion OR turbot OR turbots OR psetta OR flatfish OR flatfishes OR plaice OR pleuronectes OR platessa OR tilapia OR tilapias OR oreochromis OR sarotherodon OR common sole OR dover sole OR solea OR zebrafish OR zebrafishes OR danio OR rerio OR seabass OR dicentrarchus OR labrax OR morone OR lamprey OR lampreys OR petromyzon OR pumpkinseed OR pumpkinseeds OR lepomis OR gibbosus OR herring OR clupea OR harengus OR amphibia OR amphibian OR amphibians OR anura OR salientia OR frog OR frogs OR rana OR toad OR toads OR bufo OR xenopus OR laevis OR bombina OR epidalea OR calamita OR salamander OR salamanders OR newt OR newts OR triturus OR reptilia OR reptile OR reptiles OR bearded dragon OR pogona OR vitticeps OR iguana OR iguanas OR lizard OR lizards OR anguis fragilis OR turtle OR turtles OR snakes OR snake OR aves OR bird OR birds OR quail OR quails OR coturnix OR bobwhite OR colinus OR virginianus OR poultry OR poultries OR fowl OR fowls OR chicken OR chickens OR gallus OR zebra finch OR taeniopygia OR guttata OR canary OR canaries OR serinus OR canaria OR parakeet OR parakeets OR grasskeet OR parrot OR parrots OR psittacine OR psittacines OR shelduck OR tadorna OR goose OR geese OR branta OR leucopsis OR woodlark OR lullula OR flycatcher OR ficedula OR hypoleuca OR dove OR doves OR geopelia OR cuneata OR duck OR ducks OR greylag OR graylag OR anser OR harrier OR circus pygargus OR red knot OR great knot OR calidris OR canutus OR godwit OR limosa OR lapponica OR meleagris OR gallopavo OR jackdaw OR corvus OR monedula OR ruff OR philomachus OR pugnax OR lapwing OR peewit OR plover OR vanellus OR swan OR cygnus OR columbianus OR bewickii OR gull OR chroicocephalus OR ridibundus OR albifrons OR great tit OR parus OR aythya OR fuligula OR streptopelia OR risoria OR spoonbill OR platalea OR leucorodia OR blackbird OR turdus OR merula OR blue tit OR cyanistes OR pigeon OR pigeons OR columba OR pintail OR anas OR starling OR sturnus OR owl OR athene noctua OR pochard OR ferina OR cockatiel OR nymphicus OR hollandicus OR skylark OR alauda OR tern OR sterna OR teal OR crecca OR oystercatcher OR haematopus OR ostralegus OR shrew OR shrews OR sorex OR araneus OR crocidura OR russula OR european mole OR talpa OR chiroptera OR bat OR bats OR eptesicus OR serotinus OR myotis OR dasycneme OR daubentonii OR pipistrelle OR pipistrellus OR cat OR cats OR felis OR catus OR feline OR dog OR dogs OR canis OR canine OR canines OR otter OR otters OR lutra OR badger OR badgers OR meles OR fitchew OR fitch OR foumart or foulmart OR ferrets OR ferret OR polecat OR polecats OR mustela OR putorius OR weasel OR weasels OR fox OR foxes OR vulpes OR common seal OR phoca OR vitulina OR

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Inaccessible references

Inaccessible references include Ben et al., 2000; Burman and Sakhovskaia, 1972; Cai et al., 2017; Cai et al., 2010; Cen et al., 2001; Chai, 1990; Chen et al., 2004, 1992; D'Amico et al., 1978; Deng et al., 2006; Dolgushin et al., 1979; Dou et al., 2009; Duan et al., 2009; Ebert and Dolgushin, 1976; Echinard et al., 1989; Feng et al., 2000; Fu et al., 2009; Fumarola et al., 1972; Gao et al., 2001, 1996; Ge et al., 2009; Guo et al., 2003, 2008; Hooijmans et al., 2014; Hu et al., 2005; Huan et al., 1995; Huang et al., 2005; Hussmann et al., 1996; Jia et al., 1996; Jiang et al., 2015; Kaem et al., 1977; Kopec, 1976; Li et al., 2018, 2017, 2013, 2011, 2001, 2000; Liang et al., 2013, 1995, 1994; Lilic, 1987; Liu et al., 2006; Lou et al., 1995; Lü et al., 2000; Lu et al., 2003; Luo et al., 2002; Mao et al., 2016; Meusers et al., 1971; Mikaelian, 1988; Mikaelian and Il'ina, 1988; Mikhal'chik et al., 2006; Mou et al., 2013; Niedworok and Offierska, 1980; Niedworok and Spychalski, 1972; Osikov et al., 2018; PANG et al., 2013; Pang et al., 2004, 2003; Panosian et al., 1990; Peng et al., 2001, 1994; Qin et al., 2017, 2005; Ran et al., 2005; Shao et al., 2010; Shi and Xia, 2001; Shikhodyrev et al., 1986; Tan et al., 2004; Tang et al., 2003; Wan and Li, 2005; Wang et al., 2006b, 2005, 2004, 2003, 2001a, 2001b, 2000, 1994; Wang and Yang, 2002; Wu et al., 2001, 1997, 1994; Wu and Huang, 1996; Xiao et al., 1990; Xu et al., 2011; Xue et al., 2016; Yan et al., 1999, 1997; Yang et al., 2017a, 2017b, 2016; Yao et al., 2006, 1999; Yexiang et al., 2018; Zaets et al., 1977; Zhan et al., 2007; Zhang, 1989; Zhang et al., 2015a, 2011, 2009, 2006a, 2006b, 2006c, 2003, 2001; Zhao et al., 2005; Zheng et al., 2007; Zhou et al., 2017, 2016; Zhu et al., 2000; and Zhuo et al., 1999.

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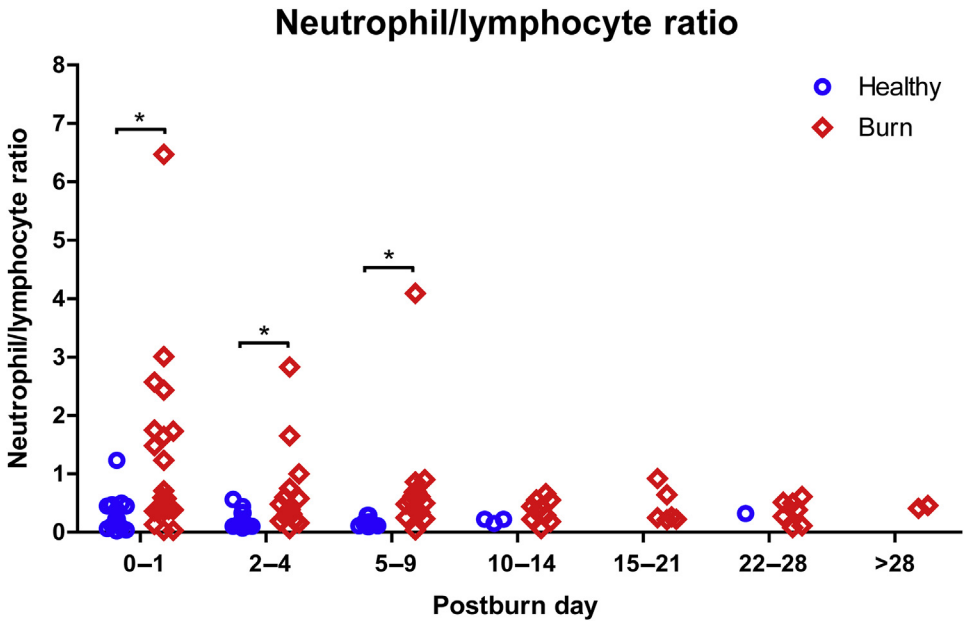

Supplementary Figure S1. Neutrophil/lymphocyte ratio. For studies that measured both neutrophil and lymphocyte numbers, the neutrophil/lymphocyte ratio was calculated for animals with burn (red) and for control animals (blue). Statistical differences between animals with burn and their control are indicated by black asterisks (Wilcoxon signed rank test: $P < 0.05$).

Supplementary Table S1. Outcome Measures and References Used in Systematic Review and Meta-Analysis

Cell Type	Outcome Data in Meta-Analysis (Number of Studies)	References in Systematic Review
Neutrophils (granulocytes, polymorphonuclear cells)	Blood immune cell count (50) Wound immune cell count (48) Migration (10) Antibacterial function (nine) ROS production (16) Inflammatory mediator production (8)	Adediran et al., 2010; Akgun et al., 2017; Alexander et al., 2006; Asko Seljavaara, 1974; Bankova et al., 2014; Baskaran et al., 2000; Bayliss et al., 2014; Begieneman et al., 2012; Bird et al., 2010; Bjornson et al., 1992; Bjornson et al., 1989; Bjornson et al., 1988; Bohr et al., 2013a, Bohr et al., 2013b; Brandenburg et al., 2019a, 2019b; Brownstein et al., 2006; Cakir et al., 2005; Calum et al., 2009; Chao et al., 2020; D'Alesandro and Gruber, 1990; de David Antoniazzi et al., 2018; Davis and Gallin, 1988; Dinescu et al., 2019; Dong et al., 1993a, 1993b; Fan et al., 2016; Fang et al., 2017; Faunce et al., 2003, 1999; Fazal et al., 2012, 2001, 1997; Fujimi et al., 2006; Gadd and Hansbrough, 1989; Gamelli et al., 1985; Gardner et al., 2014; Gómez et al., 2020; Goto et al., 2006; Gruber and D'Alesandro, 1989; Guo et al., 2015; Hansbrough et al., 1996b, 1996c; He et al., 2001; Hemmila et al., 2010; Higashimori et al., 2006; Hu and Sayeed, 2005, 2004; Inoue et al., 2018; Ipaktchi et al., 2007, 2006; Jahovic et al., 2004; Johnson et al., 2016; Kabasakal et al., 2005; Khalid et al., 2019; Kimura et al., 2008; Korkmaz et al., 2020; Kurihara et al., 2013; Lavaud et al., 1988; Li et al., 2016; Linz et al., 2017; Liu et al., 2014; Luo et al., 2013; Marano et al., 1988; Maung et al., 2008; McManus, 1983; Miles et al., 1999; Noel et al., 2010; Nomellini et al., 2012; Ny et al., 2020; Penturf et al., 1996; Perez et al., 1987; Peter et al., 1999; Piccolo et al., 1999; Pintér et al., 1999; Qian et al., 2020; Rawlingson et al., 2003, 2001; Rennekampff et al., 1995; Samonte et al., 2004; Santangelo et al., 2001; Sartorelli et al., 1991; Schmidt et al., 1983; Schwacha et al., 2019, 2005; Schwacha and Daniel, 2008; Sehirli et al., 2008; Semochkin et al., 2001; Sener et al., 2005; Shen et al., 2012; Shoup et al., 1998; Silva et al., 2013; Sulaiman et al., 2020; Till et al., 1983; Tissot et al., 1992; Toklu et al., 2007, 2006; Toth et al., 2004; Wallner et al., 1987; Wang et al., 2014; Weaver et al., 2020; Wu et al., 2010; Xiao et al., 2017, 2016, 2014, 2013; Yang et al., 2013a; Yurt and Pruitt, 1985; Yurt and Shires, 1987; Zakirova et al., 2021; Zhang et al., 2017; Zhao et al., 2009; and Zilan et al., 2003
Leukocytes (white blood cells, inflammatory cells)	Blood immune cell count (45) Wound immune cell count (14) Migration (11)	Abdallah Hajj Hussein et al., 2012; Bird et al., 2010; Bjornson et al., 1988; Brownstein et al., 2006; Burmeister et al., 2016; Calum et al., 2009; Chao et al., 2020; D'Alesandro and Gruber, 1990; de David Antoniazzi et al., 2018; Dinescu et al., 2019; Dokumcu et al., 2008; Duansak et al., 2003; Eski et al., 2001; Fiório et al., 2014; Fried et al., 1991; Fuchs et al., 2006; Fujimi et al., 2006; Gao et al., 2019; Gardner et al., 2014; Goertz et al., 2016, 2012, 2009; Gómez et al., 2018; Gruber and D'Alesandro, 1989; Gruber and Farese, 1989; Hernekamp et al., 2012; Howell et al., 2012; Ibrahim et al., 2014; Jiao et al., 2020; Jin et al., 2017; Khalid et al., 2019; Kuroiwa et al., 1990; Langer et al., 2005; Lavaud et al., 1988; Lee et al., 2011; Liu et al., 2016; Liu et al., 2015; Malakyan et al., 2004; Marano et al., 1988; Maung et al., 2008; McManus, 1983; Miles et al., 1999; Nassar et al., 2012; Noel et al., 2007; Nwariaku et al., 1996, 1995; Pallua et al., 2003; Pejnović et al., 1995; Penturf et al., 1996; Peter et al., 1999; Santangelo et al., 2001; Sartorelli et al., 1991; Schindel et al., 1997; Schwacha et al., 2005; Semochkin et al., 2001; Sheeran et al., 1998; Shippee et al., 1988; Shoup et al., 1998; Tajima et al., 2013; Tian et al., 2016; Toth et al., 2004; Zakirova et al., 2021; Zhang et al., 2020; and Zhang et al., 2015
Lymphocytes	Blood immune cell count (25)	Brownstein et al., 2006; Burleson et al., 1988, 1987; Chao et al., 2020; D'Alesandro and Gruber, 1990; Dinescu et al., 2019; Fan et al., 2016; Fujimi et al., 2006; Gamelli et al., 1985; Gardner et al., 2014; Gómez et al., 2020; Guo and Gu, 1988; Ikeuchi et al., 1981; Jabeen et al., 2019; Khalid et al., 2019; Korkmaz et al., 2017; Marano et al., 1988; Maung et al., 2008; McManus, 1983; Noel et al., 2010, 2007; Pejnović et al., 1995; Penturf et al., 1996; Sartorelli et al., 1991; Schwacha et al., 2005; Shippee et al., 1988; Toth et al., 2004; Tschöp et al., 2009; Waymack et al., 1989; Weaver et al., 2020; Xia et al., 2002; Zhang et al., 2020; Zhang et al., 2017; and Zhao et al., 2009
Monocytes	Blood immune cell count (24)	Alexis et al., 2015; Brownstein et al., 2006; Calum et al., 2009; Chao et al., 2020; Dinescu et al., 2019; Fujimi et al., 2006; Gardner et al., 2014; Gómez et al., 2020; Johnson et al., 2016; Linz et al., 2017; Madihally et al., 2002, 2001; Marano et al., 1988; Maung et al., 2008; Muthu et al., 2009; Noel et al., 2010, 2007; Penturf et al., 1996; Santangelo et al., 2001; Schwacha et al., 2005; Tajima et al., 2013; Toth et al., 2004; Weaver et al., 2020; Zakirova et al., 2021; Zhang et al., 2017; and Zhao et al., 2009
Macrophages (monocytes in wound tissue)	Wound immune cell count (21) Inflammatory mediator production (9)	Begieneman et al., 2012; Daniel et al., 2007; Dong et al., 1993b; Heinrich et al., 2003; Ibrahim et al., 2014; Inoue et al., 2018; Jabeen et al., 2019; Khalid et al., 2019; Kimura et al., 2008; Korkmaz et al., 2020; Lateef et al., 2019; Li et al., 2016; Liu et al., 2016; Liu et al., 2014; Luo et al., 2005; Maung et al., 2008; Ny et al., 2020; O'Leary et al., 2011; Osikov et al., 2014; Pejnović et al., 1995; Rani et al., 2014; Schwacha et al., 2019, 2010; Schwacha and Somers, 1998; Shallo et al., 2003; Shen et al., 2012; Silva et al., 2013; Smith and Goldman, 1972; Souza et al., 2017; Vinaik et al., 2020; Wang et al., 2011; Wang et al., 2006; Wang et al., 2002; Waymack et al., 1987; and Wu et al., 2018
Thrombocytes (platelets)	Blood immune cell count (14)	Bjornson et al., 1988; Chao et al., 2020; D'Alesandro and Gruber, 1990; Fujimi et al., 2006; Heideman, 1979; Khalid et al., 2019; Kuroiwa et al., 1990; Lavaud et al., 1988; Linz et al., 2017; Malakyan et al., 2004; Newsome and Eurenius, 1973; Noel et al., 2010; Pallua et al., 2003; Schindel et al., 1997; and Wallner et al., 1987.

(*continued*)

Supplementary Table S1. Continued

Cell Type	Outcome Data in Meta-Analysis (Number of Studies)	References in Systematic Review
Mast cells	Wound immune cell count (9)	Bankova et al., 2014; Bayat et al., 2008; Dong et al., 2015; Ibrahim et al., 2014; Lateef et al., 2019; Nishikori et al., 1998; Shiota et al., 2010; Souza et al., 2017; and Vasheghani et al., 2008.
T cells (T lymphocytes)	Blood immune cell count (9)	Burleson et al., 1988; Burleson et al., 1987; Chao et al., 2020; Daniel et al., 2007; Fan et al., 2016; Guo and Gu, 1988; Hansbrough and Gadd, 1989; Ikeuchi et al., 1981; Liu et al., 2011; Madihally et al., 2002, 2001; Organ et al., 1989; Rani et al., 2015; Rani and Schwacha, 2017; Schwacha and Daniel, 2008; Shen et al., 2012; Shippee et al., 1988; Tajima et al., 2013; Toth et al., 2004; Wu et al., 2010; Xu et al., 2017; Yang et al., 2013b; and Yao et al., 1997
$CD4^+$ T cells	Blood immune cell count (7)	Burleson et al., 1988; Chao et al., 2020; Fan et al., 2016; Madihally et al., 2001; Shippee et al., 1988; Tajima et al., 2013; and Wu et al., 2010
$CD8^+$ T cells	Blood immune cell count (7)	Burleson et al., 1988; Chao et al., 2020; Fan et al., 2016; Madihally et al., 2001; Shippee et al., 1988; Tajima et al., 2013; and Wu et al., 2010
B cells	Blood immune cell count (5)	Burleson et al., 1988; Chao et al., 2020; Fan et al., 2016; Madihally et al., 2001; Shippee et al., 1988; Tajima et al., 2013; and Wu et al., 2010
Eosinophils	Blood immune cell count (5)	Avsar et al., 2016; Fear et al., 2016; Khalid et al., 2019; Lee et al., 2011; Marano et al., 1988; Silva et al., 2013; Valvis et al., 2015; Weaver et al., 2020; and Zakirova et al., 2021
Basophils		Weaver et al., 2020
Undefined cells		Abo El-Noor et al., 2017; Daniel et al., 2007; Fear et al., 2016; Ibrahim et al., 2014; Iwashita et al., 1999; Mikhal'chik et al., 2004; Rani et al., 2014; and Schwacha et al., 2019
Phagocytes (neutrophils + monocytes)		Chakraborty et al., 2018; Guo and Gu, 1988; Noel et al., 2010; and Rani et al., 2014
Dendritic cells		Fear et al., 2016; Howell et al., 2012; and Lateef et al., 2019
NK cells		Fear et al., 2016 and Tajima et al., 2013
Langerhans cells		Bohannon et al., 2008; Chakraborty et al., 2018; and Lateef et al., 2019
NKT cells		Fear et al., 2016
PBMNCs (monocytes + lymphocytes)		Cakir et al., 2005; Groger et al., 2010; Madibally et al., 2003; Madihally et al., 2002, 2001; Rani et al., 2014; and Takahashi et al., 2004

A minimum of five articles was required for inclusion of a defined outcome measure in the meta-analysis. For cell function apoptosis, no cell type reached this minimum.