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SYSTEMATIC REVIEWS

Predictive value of cytokines for developing complications after polytrauma

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Conflict-of-interest statement: All the authors declare that they have no competing interests.

Data sharing statement: The technical appendix including the full search strategy for this systematic review is available from the corresponding author at A.E.Dekker@lumc.nl. Since this study did not involve any biostatistics, no statistical code and dataset are available.

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Abstract

AIM: To investigate posttraumatic cytokine alterations and their value for predicting complications and mortality in polytraumatized patients.

METHODS: Studies on the use of specific cytokines to predict the development of complications and mortality were identified in MEDLINE, EMBASE, Web of Science and the Cochrane Library. Of included studies, relevant data were extracted and study quality was scored.

RESULTS: Forty-two studies published between 1988 and 2015 were identified, including 28 cohort studies and 14 "nested" case-control studies. Most studies investigated the cytokines interleukin (IL)-6, IL-8, IL-10 and tumor necrosis factor (TNF-α). IL-6 seems related to muliorgan dysfunction syndrome, multiorgan failure (MOF) and mortality; IL-8 appears altered in acute respiratory distress syndrome, MOF and mortality; IL-10 alterations seem to precede sepsis and MOF; and TNF-α seems related to MOF.

CONCLUSION: Cytokine secretion patterns appear to be different for patients developing complications when compared to patients with uneventful posttraumatic course. More research is needed to strengthen the evidence for clinical relevance of these cytokines.

Key words: Multiple trauma; Cytokine; Acute respiratory distress syndrome; Sepsis; Muli-organ dysfunction syndrome; Multi-organ failure

Core tip: Early identification of patients at risk for

developing complications is one of the most challenging problems in the therapy of multiple injuries. Close monitoring of cytokine secretion patterns could give physicians an impression of the individual risk for development of complications. Further, physicians are directed to the appropriate prophylactic treatment, as well as optimal timing of surgical interventions, thereby reducing "second hits" with subsequent risks of development of sepsis and multiorgan failure. This article provides an overview of the results from literature concerning posttraumatic immune alterations leading to various complications and death.

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INTRODUCTION

The term polytrauma is used to describe a combination of serious injuries in at least two different anatomical regions. Polytraumatized patients that survive the initial impact of trauma, are confronted with an enormous host defence reaction, which is associated with morbidity and mortality. Trauma initiates a local pro-inflammatory response, encompassing the activation of effector cells, complement cascade, coagulation system, cytokines, acute phase proteins and neuroendocrine mediators[1,2]. This sequence of events is part of the physiologic response to trauma, as it serves to initiate the healing process, prevents the host from additional injury and acts as a barrier against infection[3]. Yet extensive trauma can arouse a comprehensive systemic inflammatory state known as the systemic inflammatory response syndrome (SIRS). An overactivated pro-inflammatory reaction leads to progressive sequestration of leukocytes in vital organs, predisposing patients to the development of organ failure. In an attempt to mediate these deleterious effects, immunesuppressive mediators are released. This counter regulatory response syndrome (CARS) becomes active almost immediately after the onset of SIRS[4]. Despite dampening inflammation, CARS itself may have unfavorable effects as well, as it can induce an increased susceptibility to infections and sepsis[2]. The posttraumatic immunologic alterations of combined SIRS and CARS have been termed CHAOS (cardiovascular shock, homeostasis, apoptosis, organ dysfunctions and immune suppression)[5]. With an overwhelming initial traumatic insult, an overstimulated SIRS response initiates the chaos that results in early multiorgan failure (MOF), present within 72 h after injury[2,6]. A less severe initial insult may prime immune cells while eliciting a moderate inflammatory reaction. In this setting, a second insult ("hit") may strengthen the inflammatory reaction towards immune suppression, predisposing the patient to sepsis[7,8].

Cytokines play a pivotal role in both the pro-inflammatory and the anti-inflammatory reaction to trauma[9,10]. The pro-inflammatory cytokine interleukin-6 (IL-6) is secreted by a wide range of cells including neutrophils, T- and B-lymphocytes and endothelial cells[8,11]. Release of IL-6 is enhanced after stimulation by micro-organisms and cytokines (TNF-α, IL-1β), and liberated after tissue damage and infection. The biologic activity of IL-6 includes increased T- and B-cell activation and proliferation, differentiation of cytotoxic T cells and enhanced activity of natural killer (NK) cells[12]. In addition, IL-6 mediates the induction of the acute phase response and reduces apoptosis in neutrophil granulocytes[4,11]. Combined actions lead to an effective SIRS response early after trauma. The pro-inflammatory cytokine IL-8 is an endogenous chemoattractant. Monocytes, macrophages, neutrophils and endothelial cells secrete IL-8, and its release is enhanced after stimulation with IL-1, TNF-α, C5a and LPS[9,13]. After activation, IL-8 induces expression of adhesion molecules on neutrophils and endothelial cells, which enables the migration of neutrophils to the site of production[4,9]. The anti-inflammatory cytokine IL-10 is primarily synthesized by CD4+ T_H2 lymphocytes and, to a lesser extent, by B lymphocytes, monocytes and macrophages[8]. Activated IL-10 decreases the cytokine production of T_H1 cells, reduces antigen presentation of macrophages and subsequent proliferation of T-lymphocytes, and suppresses monocyte function[4,14,15]. These actions make IL-10 one of the most important mediators in the anti-inflammatory immune response. The pro-inflammatory cytokine TNF-α is one of the first cytokines to be released after trauma. The cytokine is produced by monocytes, macrophages, lymphocytes and T lymphocytes. After secretion, TNF-α increases endothelial cell permeability and adhesion properties, and activates macrophages, NK cells and lymphocytes. TNF-α also induces the secretion of various cytokines [IL-6, -8, -10, interferon (IFN-γ)] and immunoglobulin production[7,12]. Release of excessive TNF-α ultimately leads to accumulation of leukocytes in the injured tissues. Many of these cytokines attributed to the potential development of complications in polytrauma patient. Their exact causal role has not been detected yet.

Early identification of patients at risk for developing complications is one of the most challenging problems in the therapy of multiple injuries. Close monitoring of cytokine secretion patterns could give physicians an impression of the individual risk for development of complications. Further, physicians are directed to the appropriate prophylactic treatment, as well as optimal timing of surgical interventions, thereby reducing "second hits" with subsequent risks of development of sepsis and MOF. Previous studies have acknowledged the correlation between markers of inflammation and clinical condition after polytrauma. The aim of the current review was: (1) to summarize the available

knowledge on specific cytokines that are involved in the posttraumatic immune alterations; and (2) to assess the value of cytokines for predicting the development of acute respiratory distress syndrome (ARDS), sepsis, multiorgan dysfunction syndrome (MODS), MOF and mortality.

MATERIALS AND METHODS

The systematic review was performed in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement[16]. Due to heterogeneity across the studies in terms of patient population, study design and analytical techniques used, and the small amount of studies for each biomarker-complication combination, a meta-analysis was not feasible.

Search strategy

Studies addressing the relation between complications after multiple trauma and cytokine concentrations, were identified in the following databases: MEDLINE (1988 - 18 January 2014), Embase (1988 - 18 January 2014), Web of Science (1988 - 18 January 2014) and the Cochrane Library (to Issue 1, 2014). The search strategy was developed by an information specialist, and carried out using various combinations of the key words "multiple trauma", "cytokines" and the complications "systemic inflammatory response sydrome (SIRS)", "ARDS", "sepsis", "MODS", "MOF" and "mortality". In addition, forward citation searches of selected studies and literature reviews were carried out. The initial search was not limited by language, publication date and type of publication. In February 2016, an additional literature search of the mentioned databases was carried out. One relevant new article was found.

Outcome definitions

Primary outcomes were the development of one or more of the following complications: (1) ARDS, determined in concordance with the American-European Consensus Conference 1994 definitions[17]; (2) sepsis, diagnosed when SIRS (defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference 1992[18]) occurred in combination with a septic focus or positive blood culture; (3) MODS; and (4) MOF, in the included studies diagnosed based on different scoring systems[19-24]. The secondary outcome was mortality during a predetermined follow-up period of individual studies.

Study selection

Studies were scanned for eligibility based on title and abstract. Subsequently, eligibility of selected studies was assessed by retrieving the full text of the article. Inclusion criteria were prospective or retrospective cohort, case-control and cross-sectional studies including at least 10 adult multiple trauma patients (ISS $\geqslant$ 16). Excluded were articles in other language than English or German, animal studies and *ex vivo* studies, studies involving pediatric populations, case reports, review articles and letters/editorials. Studies not elaborating on the primary or secondary outcomes investigated in this review were also excluded. In addition, studies measuring cytokine concentrations in samples other than serum (*e.g.*, wound exsudate, broncho-alveolar lavage fluid) were not eligible for inclusion, as local alterations in concentration may not reflect the systemic changes in the immune reaction.

Data extraction

The following data were extracted from included studies: Title, study design, date of publication, size of study population, patient demographics, incidence of complications and mortality, follow-up period, type of cytokines studied, mean cytokine concentrations measured at specific moments during follow-up, and cut-off points with sensitivity and specificity. Data were extracted from figures when raw data were not available. In the case of duplicate publications, the most relevant or informative article was chosen.

Quality assessment

The quality of included studies was critically evaluated with the strengthening the reporting of observational studies in epidemiology (STROBE) statement[25].

Biostatistics statement

In this review of the literature no biostatistical methods were used. For this reason, no biomedical statistician was involved for statistical review.

RESULTS

Identification of studies

After exclusion of duplicate studies, the literature search yielded 730 potentially relevant articles. One hundred and thirty-eight articles passed the first screening and were retrieved for closer examination. Of the retrieved articles, 40 were eligible for study inclusion. The full text of six potentially relevant studies could not be obtained, which were therefore excluded from the analysis. Seven citations were found assessing reference lists of the included studies. One relevant article was encountered in the additional search carried out in 2016. The study selection procedure is outlined in Figure 1.

Study characteristics

The 42 included articles consisted of 28 cohort studies[3,13,26-51] and 14 "nested" case-control studies[11,14,52-63]. Two studies were retrospective[14,52]; the other 40 studies were prospective in study design. Studies were published between 1988 and 2015, and together included 5756 patients. The development of ARDS in relation to cytokine levels was investigated in seven studies; sixteen studies determined cytokine concentrations in sepsis; MODS development was assessed in ten studies; and eleven studies reported cytokine

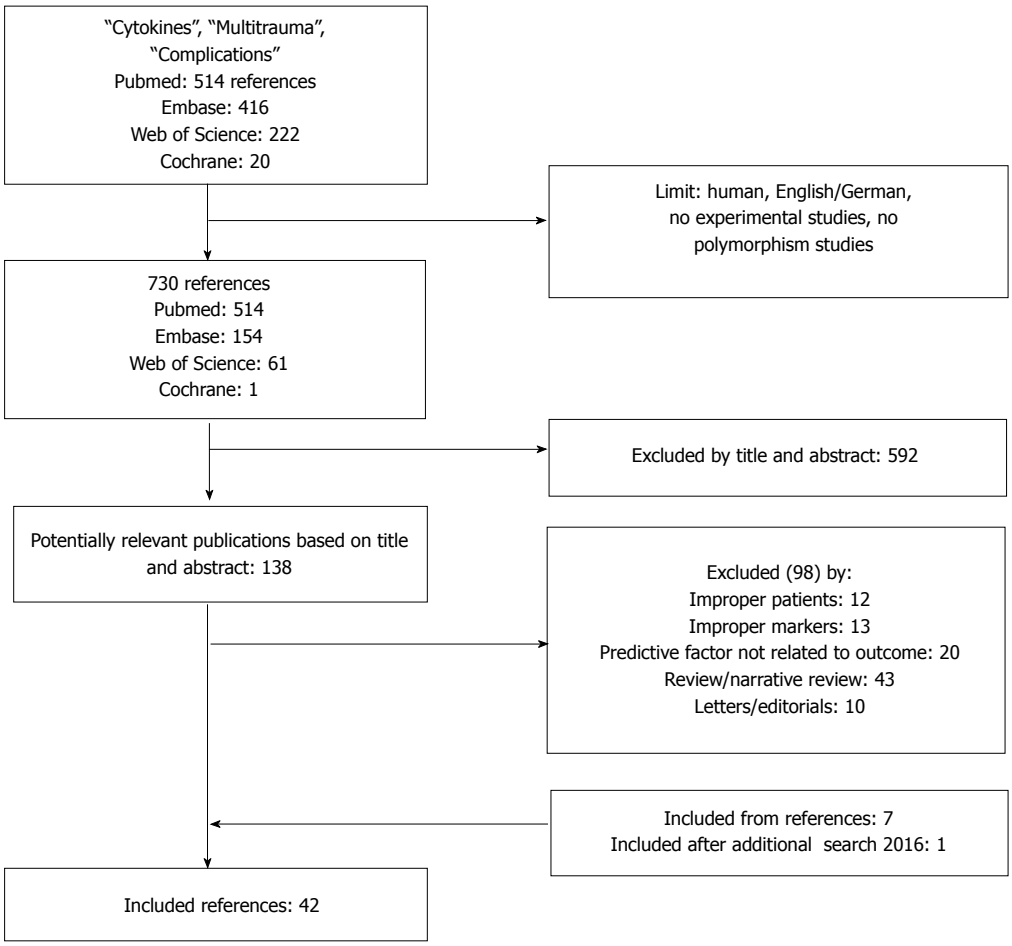

Figure 1 Results of the stepwise literature review procedure.

alterations in MOF. Twenty studies investigated the relation between cytokine concentrations and mortality. Only seven studies reported a cytokine cut-off value for the development of complications, five of which stated sensitivity (and specificity) for the cut-off value. Ten studies reported some kind of prediction value for the investigated cytokines (*i.e.*, odds ratio, area under the curve, sensitivity and specificity, 95%CI and positive/negative predictive value). All included studies are listed in Table 1. The overall study quality according to the STROBE statement was good, with a median total score of 18 points (range 12-24), suggesting a low risk of bias.

Value of main cytokine concentrations for predicting complications

IL-6: (1) ARDS; two studies[37,45] could not relate ARDS to IL-6 concentration alterations, whereas two other studies[48,51] found a positive correlation (Table 2); (2) Sepsis; five studies[35,41,46,47,53] found an increased IL-6 production to be predictive for the development of sepsis, whereas five other studies[28,29,38,39,55] did not (Table 3); (3) MODS; all five prospective cohort studies[3,28,34,46,51] concluded that IL-6 is markedly increased in the early development of MODS (Table 4); and (4) MOF; of the nine prospective studies, six[13,27,32,33,36,56] studies found a positive correlation between increased serum concentrations and development of MOF. Three[11,42,62] investigators demonstrated an elevated IL-6 in MOF patients, which was not predictive according to these studies (Table 5). Also, IL-6 tends to be higher in non-survivors (Table 6).

IL-8: (1) Two prospective cohort studies[37,48] reported a positive correlation between increased serum IL-8 concentrations and development of ARDS, whereas one[45] found no predictive value; (2) Two studies[38,55] reported that IL-8 was not significantly different between patients developing sepsis and those with an uneventful posttraumatic course; (3) One cohort study[3] found a higher IL-8 serum concentration in patients with MODS, which could however not predict the development of multiorgan dysfunction; and (4) Of the six included studies, four prospective studies[27,32,36,56] concluded that IL-8 is significantly higher in MOF. Two prospective studies[11,42] also found a significantly increased serum concentration, but concluded that this could not be translated into a predictive value for adverse outcome. Further, IL-8 concentrations seemed elevated in non-survivors.

Table 1 Overview of included studies, the studied cytokines and the outcome parameters (acute respiratory distress syndrome, sepsis, muli-organ dysfunction syndrome, multi-organ failure, mortality)

No.	Ref.	Year	Design	No pts. (control)	Cytokines	ARDS (%)	Sepsis (%)	MODS (%)	MOF (%)	Mortality (%)
1	Billeter *et al*[35]	2009	P-coh	1032	IL-6					10%
2	Bogner *et al*[36]	2009	P-coh	58	IL-6, -8, -10				74%	19%
3	Cook *et al*[58]	2013	P-cc	83 (18)	G-CSF		7%			7%
4	Cuschieri *et al*[34]	2010	P-coh	152	IL-6			37%		5%
5	Donnelly *et al*[37]	1994	P-coh	15	IL-6, -8, -1β; TNF-α	49%				33%
6	Dresing *et al*[26]	2004	P-coh	30	IL-6; TNF-α			13%		19%
7	Egger *et al*[38]	2004	P-coh	26	IL-6, -8		35%			
8	Flores *et al*[39]	2001	P-coh	43	IL-6		49%			16%
9	Frangen *et al*[59]	2008	P-cc	71 (25)	IL-17, -6					22%
10	Frank *et al*[11]	2002	P-cc	77 (15)	IL-6, -8					9%
11	Frink *et al*[3]	2009	P-coh	143	IL-1β, -6, -8, -10; TNF-α		29%	17%		15%
12	Gebhard *et al*[40]	2000	P-coh	94	IL-6					19%
13	Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69 (10)	IL-6, -8; TNF-α, IFN-γ		62%			35%
14	Gouel-Chéron *et al*[53]	2012	P-cc	100 (18)	IL-6, -10		37%			5%
15	Haasper *et al*[28]	2010	P-coh	94	IL-6		16%	22%		13%
16	Hayakawa *et al*[31]	2011	P-coh	45	TNF-α			53%		25%
17	Heizmann *et al*[52]	2008	R-cc	195 (10)	IL-2, -4, -10, -11, -12, -18; IFN-γ					19%
18	Jastrow *et al*[32]	2009	P-coh	48	IL-6, -8, -10, -1β, -2, -4, -12; TNF-α				23%	17%
19	Keel *et al*[41]	2009	P-coh	83	IL-6		40%			12%
20	Lausevic *et al*[33]	2008	P-coh	65	IL-6, -10		62%		55%	51%
21	Lausevic *et al*[29]	2010	P-coh	65	IL-6, -10		63%			51%
22	Law *et al*[42]	1994	P-coh	13	IL-6, -8; TNF-α				46%	23%
23	Lendemans *et al*[13]	2004	P-coh	16	IL-6, -10; TNF-α				56%	
24	Liener *et al*[43]	2002	P-coh	94	IL-8	0%	0%		0%	19%
25	Livingston *et al*[44]	1988	P-coh	20	IFN-γ		30%			15%
26	Maier *et al*[27]	2007	P-coh	251	IL-6, -8, -10				34%	12%
27	Meade *et al*[45]	1994	P-coh	25	IL-6, -8; TNF-α	36%				
28	Menges *et al*[50]	1999	P-coh	68	IL-10, -1; TNF-α		25%		25%	1%
29	Mommsen *et al*[30]	2009	P-coh	55	IL-18		42%	13%		13%
30	Neidhardt *et al*[54]	1997	P-cc	417 (137)	IL-10	5%	11%	22%		22%
31	Oberholzer *et al*[46]	2000	P-coh	1276	IL-6, IL-10		14%	40%		7%
32	Partrick *et al*[56]	1996	P-cc	27 (6)	IL-6, -8				33%	7%
33	Paunel-Görgülü *et al*[47]	2011	P-coh	47 (17)	IL-6		38%			11%
34	Raymondos *et al*[48]	2012	P-coh	24	IL-6, -8, -1β, TNF-α	29%				4%
35	Roetman *et al*[60]	2008	P-cc	229 (110)	IL-18, -4; IFN-γ					16%
36	Schinkel *et al*[61]	2005	P-cc	216 (110)	IL-11				4%	16%
37	Sherry *et al*[14]	1996	R-cc	66 (10)	IL-10	8%	39%			2%
38	Sousa *et al*[51]	2015	P-coh	99	IL-6, -10; TNF-α	19%		34%		28%
38	Spielmann *et al*[57]	2001	P-cc	47 (15)	TNF-α	11%	30%	51%		23%
39	Svoboda *et al*[62]	1994	P-cc	42 (12)	IL-1β, -2, -6; TNF-α				33%	26%
40	Wick *et al*[49]	2000	P-coh	37	IL-12			11%		16%
41	Yagmur *et al*[63]	2005	P-cc	99 (10)	IL-1, -2, -6, -8; TNF-α					17%

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; Pts: Patients; Y: Yes; N: No.

IL-10: (1) Three studies, two prospective[54,57] and one retrospective[14], could not relate the serum IL-10 concentrations to the development of ARDS. One study[51] found IL-10 to be significantly higher in patients with ARDS; (2) Of the five reviewed studies, three prospective[29,50,54] and one retrospective study[14] found the IL-10 concentration to be predictive for the development of sepsis, whereas one prospective study[53] did not; (3) Two studies[51,54] reported IL-10 to be significantly elevated in patients with MODS, and two studies[3,57] could not find an association between the cytokine and development of MODS; and (4) According to five studies[13,32,33,36,50] the serum IL-10 concentration was significantly higher in MOF patients. One study showed no significant elevation[27].

TNF-α: (1) Three studies found no relation between TNF-α and development of ARDS[37,45,51]; (2) One study[55] concluded that concentrations were not related to development of sepsis, while one study[50] found significantly increased concentrations in septic patients; (3) Of the four studies reporting on TNF-α concentrations after trauma, two studies[31,51] found TNF-α to be related to the development of MODS, and two studies[3,57] could not relate serum concentrations

Table 2 Value of cytokine concentrations for predicting acute respiratory distress syndrome

Ref.	Year	Design	No pts.	ARDS *n* (%)	Predicts ARDS	Results
IL-6						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	N	[IL-6] is not significantly different in ARDS
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[IL-6] is higher in patients with ARDS after onset of symptoms; does not predict development of ARDS
Raymondos *et al*[48]	2012	P-coh	24	7 (29%)	Y	[IL-6] is significantly higher in patients at high risk for ARDS
Sousa *et al*[51]	2015	P-coh	99	19 (19%)	Y	[IL-6] is significantly higher at 72 h post injury
IL-8						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	Y	[IL-8] is significantly higher in patients with ARDS, starting at 16 h post injury
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[IL-8] is higher in patients with ARDS after onset of symptoms; does not predict development of ARDS
Raymondos *et al*[48]	2012	P-coh	24	7 (29%)	Y	[IL-8] is significantly higher in patients at high risk for ARDS
IL-10						
Neidhardt *et al*[54]	1997	P-cc	417	19 (5%)	N	[IL-10] is not related to the development of ARDS
Sherry *et al*[14]	1996	R-cc	66	5 (8%)	N	[IL-10] is not related to the development of ARDS
Sousa *et al*[51]	2015	P-coh	99	19 (19%)	Y	[IL-10] is significantly higher in patients with ARDS upon admission, at 24 + 48 + 72 h post injury
Spielmann *et al*[57]	2001	P-cc	47	5 (11%)	N	[IL-10] is not related to the development of ARDS
TNF-α						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	N	[TNF-α] below detection limit
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[TNF-α] below detection limit
Sousa *et al*[51]	2015	P-coh	99	19 (19%)	N	[TNF-α] is not related to the development of ARDS
IL-1β						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	N	[IL-1β] below detection limit
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[IL-1β] below detection limit

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; Pts: Patients; Y: Yes; N: No.

Table 3 Value of cytokine concentrations for predicting sepsis

Ref.	Year	Design	No pts.	Sepsis *n* (%)	Diagnostic tests	Predicts sepsis	Results
IL-6							
Billeter *et al*[35]	2009	P-coh	1032			Y	[IL-6] is significantly higher in sepsis between days 3-7
Egger *et al*[38]	2004	P-coh	26	9 (35%)		N	[IL-6] is significantly higher in sepsis before clinical manifestations; does not predict sepsis
Flores *et al*[39]	2001	P-coh	43	21 (49%)		N	[IL-6] is not significantly altered in sepsis
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)	ROC AUC 0.500 (95%CI: 0.304-0.696, $P > 0.05$)	N	[IL-6] is not related to the development of sepsis
Gouel-Chéron *et al*[53]	2012	P-cc	100	37 (37%)	> 67.1 pg/mL: Sensitivity 85%; specificity 73%	Y	[IL-6] > 67.1 pg/mL is predictive for sepsis on days 1 + 2 (OR = 10.9)
Haasper *et al*[28]	2010	P-coh	94	15 (16%)		N	[IL-6] is not significantly different in sepsis
Keel *et al*[41]	2009	P-coh	83	33 (40%)		Y	[IL-6] is significantly higher in sepsis on days 5 + 14
Lausevic *et al*[33]	2010	P-coh	65	41 (63%)		N	[IL-6] is not predictive for sepsis
Oberholzer *et al*[46]	2000	P-coh	1276	179 (14%)		Y	[IL-6] is significantly higher in septic patients
Paunel-Görgülü *et al*[47]	2011	P-coh	47	18 (38%)	AUC ROC 0.79 (day 5 post injury)	Y	[IL-6] is significantly elevated on days 5 + 9 in sepsis
IL-8							
Egger *et al*[38]	2004	P-coh	26	9 (35%)		N	[IL-8] is not significantly altered in sepsis
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)	AUC ROC 0.453 (95%CI: 0.254-0.652, $P > 0.05$)	N	[IL-8] is not predictive for sepsis
IL-10							
Gouel-Chéron *et al*[53]	2012	P-cc	100	37 (37%)		N	[IL-10] is not related to the development of sepsis
Lausevic *et al*[33]	2010	P-coh	65	41 (63%)		Y	[IL-10] is significantly lower in sepsis on days 1 + 2
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-10] is significantly higher in sepsis and MOF after 6 d

Neidhardt *et al*[54]	1997	P-cc	417	45 (11%)		Y	[IL-10] is significantly higher in sepsis on days 1 + 3 + 5 + 7 + 10 + 14 + 21
Sherry *et al*[14]	1996	R-cc	66	26 (39%)		Y	[IL-10] is significantly higher in sepsis
TNF-α							
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)	AUC ROC 0.466 (95%CI: 0.274-0.657, $P > 0.05$)	N	[TNF-α] is not related to the development of sepsis
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[TNF-α] is significantly higher in sepsis and MOF after 8 d
IFN-γ							
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)		N	[IFN-γ] below detection limit
Livingston *et al*[44]	1988	P-coh	20	6 (30%)		Y	[IFN-γ] is markedly lower in sepsis after 14 d
G-CSF							
Cook *et al*[58]	2013	P-cc	83	6 (7%)		Y	[G-CSF] > 500 pg/mL is significantly associated with sepsis
IL-18							
Mommsen *et al*[30]	2009	P-coh	55	23 (42%)		Y	[IL-18] is significantly higher in sepsis on days 3-6 post injury
IL-1							
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-1] is significantly higher in sepsis and MOF on days 3 + 5 + 6 + 9 - 13

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; ROC: Receiver operating characteristic; AUC: Area under curve; Pts: Patients; Y: Yes; N: No.

Table 4 Value of cytokine concentrations for predicting muli-organ dysfunction syndrome

Study	Year	Design	No pts.	MODS *n* (%)	Diagnostic tests	Predicts MODS	Results
IL-6							
Cuschieri *et al*[34]	2010	P-coh	152	29 (37%)	> 350 pg/mL: Sensitivity 79%, specificity 76%; OR = 3.87 (95%CI: 1.13-11.19)	Y	[IL-6] > 350 pg/mL is highly associated with MODS
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.35$; > 761.7 pg/μL: Sensitivity 16.7%, specificity 98.3%	Y	[IL-6] > 76.6 pg/μL is associated with MODS with accuracy of 84.7%
Haasper *et al*[28]	2010	P-coh	94	21 (22%)		Y	[IL-6] is significantly higher in MODS on days 1 + 7
Oberholzer *et al*[46]	2000	P-coh	1276	516 (40%)		Y	[IL-6] is significantly higher in (severe) MODS
Sousa *et al*[51]	2015	P-coh	99	34 (34%)	> 294 pg/mL: AUC ROC 0.769 (95%CI: 0.414-0.736)	Y	[IL-6] > 294 pg/mL is associated with MODS at 48 + 72 h post injury
IL-8							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.53$; sensitivity 0%	N	[IL-8] is significantly higher in MODS; does not predict development of MODS
IL-10							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.31$; sensitivity 0%	N	[IL-10] is significantly higher in MODS; does not predict development of MODS
Neidhardt *et al*[54]	1997	P-cc	417	92 (22%)		Y	[IL-10] is significantly higher in MODS on days 1 + 3 + 5 + 7 + 10 + 14 + 21 post injury
Spielmann *et al*[57]	2001	P-cc	47	24 (51%)		N	[IL-10] is not related to the development of MODS
Sousa *et al*[51]	2015	P-coh	99	34 (34%)	> 4.93 pg/mL: AUC ROC 0.700 (95%CI: 0.506-0.841)	Y	[IL-10] > 4.93 pg/mL is associated with MODS at 24 + 72 h post injury
TNF-α							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.32$; sensitivity 0%	N	[TNF-α] is significantly higher in MODS; does not predict development of MODS
Hayakawa *et al*[31]	2010	P-coh	45	24 (53%)		Y	[TNF-α] is significantly higher in MODS on days 3 + 5
Sousa *et al*[51]	2015	P-coh	99	34 (34%)		Y	[TNF-α] is associated with MODS at 48 h post injury
Spielmann *et al*[57]	2001	P-cc	47	24 (51%)		N	[TNF-α) is not associated with MODS
IL-1β							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.00$; sensitivity 0%	N	[IL-1β] is not related to development of MODS
IL-12							
Wick *et al*[49]	2000	P-coh	37	4 (11%)		Y	[IL-12] is significantly lower in patients with MODS
IL-18							
Mommsen *et al*[30]	2009	P-coh	55	7 (13%)		Y	[IL-18] is significantly higher in MODS on days 2 + 3 + 6 + 7 + 9 + 10 + 13 + 14
MIF							
Hayakawa *et al*[31]	2010	P-coh	45	24 (53%)		Y	[MIF] is significantly higher in MODS

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; ROC: Receiver operating characteristic; AUC: Area under curve; *r*: Correlation coefficient between cytokine and development of MODS; MODS: Muli-organ dysfunction syndrome; Pts: Patients; Y: Yes; N: No.

Table 5 Value of cytokine concentrations for predicting multi-organ failure

Ref.	Year	Design	No pts.	MOF *n* (%)	Diagnostic tests	Predicts MOF	Results
IL-6							
Bogner *et al*[36]	2009	P-coh	58	43 (74%)		Y	[IL-6] is significantly higher in MOF at 0 - 24 + 72 h
Frank *et al*[11]	2002	P-cc	77		*r* = 0.25 on day 2	N	[IL-6] is significantly higher in MOF; no reliable predictor due to low *r*
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	AUC ROC 0.816; (IL-6) > 0.861 pg/mL: sensitivity 57%, PPV 100%	Y	[IL-6] > 0.861 pg/mL is highly predictive for MOF
Lausevic *et al*[33]	2008	P-coh	65	36 (55%)		Y	[IL-6] is significantly higher in MOF on all days of hospitalization
Lendemans *et al*[13]	2004	P-coh	16	9 (56%)		Y	[IL-6] is significantly higher in MOF after two weeks
Law *et al*[42]	1994	P-coh	13	6 (46%)		N	[IL-6] is elevated in MOF, does not predict MOF
Maier *et al*[27]	2007	P-coh	251	85 (34%)	AUC ROC 0.70 for late-onset MOF	Y	[IL-6] is predictive for (late) MOF
Partrick *et al*[56]	1996	P-cc	27	9 (33%)		Y	[IL-6] is significantly higher in MOF at 12 + 36 h
Svoboda *et al*[62]	1994	P-cc	42	14 (33%)		N	[IL-6] is higher in MOF at day 1, does not predict MOF
IL-8							
Bogner *et al*[36]	2009	P-coh	58	43 (74%)		Y	[IL-8] is significantly higher in MOF from 0-72 h
Frank *et al*[11]	2002	P-cc	77		*r* = 0.32 on day 2	N	[IL-8] is significantly higher in MOF; not reliable due to low *r*
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)		Y	[IL-8] is significantly higher in MOF from 0-24 h
Law *et al*[42]	1994	P-coh	13	6 (46%)		N	[IL-8] is elevated in MOF, does not predict MOF
Maier *et al*[27]	2007	P-coh	251	85 (34%)	AUC ROC 0.69 for late-onset MOF	Y	[IL-8] is predictive for (late) MOF
Partrick *et al*[56]	1996	P-cc	27	9 (33%)		Y	[IL-8] is significantly higher in MOF at 12 + 36 + 84 h
IL-10							
Bogner *et al*[36]	2009	P-coh	58	43 (74%)		Y	[IL-10] is significantly higher in MOF in early post-injury phase (< 12 h)
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	AUC ROC 0.776; (IL-10) > 38.6 pg/mL: Sensitivity 71%, PPV 77%	Y	[IL-10] > 38.6 pg/mL is predictive for MOF
Lausevic *et al*[33]	2008	P-coh	65	36 (55%)		Y	[IL-10] is significantly higher in MOF in very early post injury phase
Lendemans *et al*[13]	2004	P-coh	16	9 (56%)		Y	[IL-10] is significantly higher in MOF on days 3 + 4
Maier *et al*[27]	2007	P-coh	251	85 (34%)	AUC ROC 0.60 for late-onset MOF	N	[IL-10) is not predictive for MOF
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-10] is significantly higher in sepsis and MOF after 6 d
TNF-α							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)		Y	[TNF-α] is significantly higher in MOF from 2 – 6 + 10 – 24 h
Lendemans *et al*[13]	2004	P-coh	16	9 (56%)		Y	[TNF-α] is significantly higher in MOF on days 7 + 8 + 10 + 11
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[TNF-α] is significantly higher in sepsis and MOF after 8 d
Svoboda *et al*[62]	1993	P-cc	42	14 (33%)		Y	[TNF-α] is higher in MOF, but only after onset of symptoms
IL-1(β)							
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-1] is significantly higher in sepsis and MOF on days 3 + 5 + 6 + 9 - 13
Svoboda *et al*[62]	1994	P-xx	42	14 (33%)		N	[IL-1β] is not related to MOF
IL-2							
Svoboda *et al*[62]	1994	P-cc	42	14 (33%)		N	[IL-2] is not related to MOF
IP-10							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	> 889.9 pg/mL has a sensitivity of 71% and PPV of 100%	Y	[IP-10] is highly predictive for MOF (AUC ROC 0.939)
Eotaxin							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	> 193.8 pg/mL has a sensitivity of 71% and PPV of 62%	Y	[Eotaxin] is highly predictive for MOF (AUC ROC 0.810)
MIP-1β							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	> 248.6 pg/mL has a sensitivity of 71% and PPV of 77%	Y	[MIP-1β] is highly predictive for MOF (AUC ROC 0.871)
IL-11							
Schinkel *et al*[61]	2005	P-cc	216	9 (4%)		N	[IL-11[is not significantly different in MOF

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; ROC: Receiver operating characteristic; AUC: Area under curve; *r*: Correlation coefficient between cytokine and development of MOF; PPV: Positive predictive value; MOF: Multi-organ failure; Pts: Patients; Y: Yes; N: No.

Table 6 Value of cytokine concentrations for predicting mortality

Ref.	Design	No pts.	Mortality *n* (%)	Follow-up	Diagnostic tests	Predicts mortality	Results
IL-6							
Bogner *et al*[36]	P-coh	58	11 (19%)	90 d		Y	[IL-6] is significantly higher in non-survivors at 0 + 6 h
Cuschieri *et al*[34]	P-coh	152	4 (5%)	In-hospital		N	[IL-6] is not significantly higher in non-survivors
Dresing *et al*[26]	P-coh	30	6 (19%)	29 d		Y	[IL-6] is significantly higher in non-survivors on days 3 + 5
Frink *et al*[3]	P-coh	143	21 (15%)	In-hospital	> 2176.0 pg/mL: Sensitivity 28.6%, specificity 100% on day 1	Y	[IL-6] is highly predictive for non-survival (AUC ROC 0.858)
Frangen *et al*[59]	P-cc	71	16 (22%)	In-hospital		Y	[IL-6] is significantly higher in non-survivors
Gebhard *et al*[40]	P-coh	94	18 (19%)	In-hospital		Y	[IL-6] is significantly higher in non-survivors at 4 + 6 + 12 h post injury
Maier *et al*[27]	P-coh	251	29 (12%)	In-hospital	AUC ROC 0.60	N	[IL-6] is not predictive for non-survival
Sousa *et al*[51]	P-coh	99	28 (28%)	72 h	> 276 pg/mL: AUC ROC2 0,775 (95%CI: 0.591-0.960)	Y	[IL-6] > 276 pg/mL is significantly correlated with non-survival
Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital	> 400 pg/mL has a sensitivity of 100%	Y	[IL-6] > 400 pg/mL is significantly correlated with non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		Y	[IL-6] is significantly elevated in non-survivors
IL-8							
Bogner *et al*[36]	P-coh	58	11 (19%)	90 d		Y	[IL-8] is significantly higher in non-survivors at 6 + 24 h
Liener *et al*[43]	P-coh	94	18 (19%)	15 d		Y	[IL-8] is significantly higher in non-survivors from 30 min-24 h
Maier *et al*[27]	P-coh	251	29 (12%)	In-hospital	AUC ROC 0.45	N	[IL-8] is not predictive for non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		Y	[IL-8] is significantly elevated in non-survivors
IL-10							
Bogner *et al*[36]	P-coh	58	11 (19%)	90 d		Y	[IL-10] is significantly higher in non-survivors at 72 h post injury
Gouel-Chéron *et al*[53]	P-cc	100	5 (5%)	14 d		Y	[IL-10] is significantly higher in non-survivors when detectable on days 1 + 2
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d		N	[IL-10] tends towards lower levels in non-survivors; not significant
Maier *et al*[27]	P-coh	251	29 (12%)	In-hospital	AUC ROC 0.51	N	[IL-10] is not predictive for non-survival
Neidhardt *et al*[54]	P-cc	417	92 (22%)	21 d		Y	[IL-10] is significantly increased in non-survivors on days 1 + 3
Sherry *et al*[14]	R-cc	66	1 (2%)	50 d		N	[IL-10] is not related to non-survival
Sousa *et al*[51]	P-coh	99	28 (28%)	72 h	> 8.24 pg/mL: AUC ROC 0.871 (95%CI: 0.715-1.000)	Y	[IL-10] > 8.24 pg/mL is associated with non-survival at 48 + 72 h post injury
TNF-α							
Dresing *et al*[26]	P-coh	30	6 (19%)	29 d		N	[TNF-α] is not significantly elevated in non-survivors
Sousa *et al*[51]	P-coh	99	28 (28%)	72 h		N	[TNF-α] is not significantly elevated in non-survivors
Spielmann *et al*[57]	P-cc	47	11 (23%)	6 d		N	[TNF-α] is not significantly elevated in non-survivors
Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital		Y	[TNF-α] is significantly elevated in non-survivors
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		N	[TNF-α] is not significantly elevated in non-survivors
IL-18							
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d		N	[IL-18] tends towards lower levels in non-survivors; not significant
Mommsen *et al*[30]	P-coh	55	7 (13%)	14 d		Y	[IL-18] is significantly increased in non-survivors on days 2-7
Roetman *et al*[60]	P-cc	229	36 (16%)	30 d		N	[IL-18] median value is significantly lower in non-survivors
IL-2							
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d		N	[IL-2] tends towards lower levels in non-survivors; not significant
Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital		N	[IL-2] is not related to non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		Y	[IL-2] is significantly increased in non-survivors
IL-1							

Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital	N	[IL-1] is not related to non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d	N	[IL-1] is not related to non-survival
IL-12						
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IL-12] tends towards lower levels in non-survivors; not significant
Wick *et al*[49]	P-coh	37	6 (16%)	In-hospital	Y	[IL-12] is significantly lower in non-survivors
IL-11						
Schinkel *et al*[61]	P-cc	216	34 (16%)	In-hospital	N	[IL-11] is lower in non-survivors, only reaching significance after week 4
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IL-11] tends towards lower levels in non-survivors; not significant
IL-17						
Frangen *et al*[59]	P-cc	71	16 (22%)	In-hospital	N	[IL-17] is not related to non-survival
IL-4						
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IL-4] tends towards lower levels in non-survivors; not significant
Roetman *et al*[60]	P-cc	229	36 (16%)	30 d	N	[IL-4] is not related to mortality
IFN-γ						
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IFN-γ] tends towards lower levels in non-survivors; not significant
Roetman *et al*[60]	P-cc	229	36 (16%)	30 d	N	[IFN-γ] inconsistently detectable

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; AUC: Area under the receiver operating characteristic (ROC) curve; Pts: Patients; Y: Yes; N: No.

to MODS; and (4) Four studies[13,32,50,62] showed that patients with MOF had significantly higher TNF-α concentrations compared to patients with uneventful course, although Svoboda *et al*[62] found no predictive value for the cytokine.

DISCUSSION

Polytraumatized patients are at risk for the development of various complications, leading to considerable morbidity and mortality. Early identification of "high risk" patients could improve outcome after accidental injury, because physicians are directed to the appropriate treatment. Further, close monitoring of the immune response could direct physicians to the appropriate timing of surgical interventions, thereby reducing "second hits" with subsequent development of sepsis and organ failure. The aim of the present review was to summarize the knowledge on cytokines predicting the development of ARDS, sepsis, MODS, MOF and mortality. According to the investigated studies, some cytokines seem to predict specific complications: Patients with ARDS seem to have higher IL-8 concentrations; IL-10 secretion seems increased in septic patients; and MODS/MOF development is preceded by an enhanced IL-6, IL-8, IL-10, and TNF-α release. With respect to the other cytokines studied (IFN-γ, G-CSF, IL-1β, -2, -4, -11, -12, -17, -18, MIF, MIP-1β, eotaxin, IP-10), study results are either inconsistent, or the small amount of current evidence makes an objective conclusion for the present study impossible.

IL-6

Release of IL-6 is enhanced after stimulation by micro-organisms and cytokines (TNF-α, IL-1β)[7,8]. It is liberated after tissue damage and infection. The relatively late release and long half-life of IL-6 renders the cytokine a convenient parameter for clinical monitoring of the immune response of individual patients. The conflicting results of the reviewed studies lead to the conclusion that IL-6 cannot be used as a marker for ARDS and sepsis; elevated IL-6 concentrations do appear to precede the development of MODS, MOF and mortality. In future, physicians might therefore use IL-6 as a predictor of MODS, MOF and mortality in polytraumatized patients.

IL-8

IL-8 induces expression of adhesion molecules, thereby enabling migration of neutrophils to the site of production[4,9]. Production of IL-8 takes place early in the inflammatory response and can persist for days or weeks[13]. According to the reviewed studies, IL-8 is higher in patients developing ARDS, MOF and in non-survivors. Of note, when IL-8 is used to investigate the development of ARDS, measuring local concentrations in bronchoalveolar lavage fluid generally leads to earlier identification of patients at risk[64-67]. The causal relation between the chemotaxis IL-8 exerts on PMN's, and subsequent autodestructive changes in remote organs leading to ARDS and MOF[64], likely explains the consistent results of included studies. In line with these results, IL-8 might be used to identify patients prone to develop ARDS and MOF. Such a predictive value could not be demonstrated for the development of sepsis and MODS.

IL-10

IL-10 decreases cytokine production of T_H1 cells and reduces antigen presentation of macrophages and subsequent proliferation of T lymphocytes[14]. Release of high amounts of IL-10 occurs rapidly, generally within 60 min after trauma[54]. According to our study, an

enhanced IL-10 secretion is related to the development of sepsis and MOF. Clearly, a vigorous anti-inflammatory IL-10 release makes the host susceptible to infections with subsequent sepsis and (sepsis-related) MOF. Therefore, IL-10 concentrations might direct physicians to the patients prone to develop sepsis and MOF. Concentrations of IL-10 could not be related to the development of ARDS, MODS and mortality.

TNF-α

The pro-inflammatory cytokine TNF-α is one of the first cytokines to be released after trauma[4]. Peak concentrations of TNF-α can be observed within one to two hours after trauma. Previous studies have demonstrated a positive correlation between elevated TNF-α and poor outcome[68-70]. However, as reported in this review, the elevation of TNF-α could only be related to the development of MOF. This might be explained by the very short half-time of the cytokine (14-18 min), suggesting that peak concentrations early in the posttraumatic course have already returned to baseline by the time a septic event and subsequent organ failure is recognized[2,9,13].

Other cytokines

According to Cook *et al*[58], elevation of G-CSF significantly related to the development of hospital-acquired pneumonia. Wick *et al*[49] demonstrated that all patients with continuous decreased IL-12 levels died from septic MOF; comparable findings were demonstrated by Hensler *et al*[71]. Increased IL-12 production could, however, have unfavorable effects as well[72,73]. According to previous studies, IL-18 release is significantly correlated with sepsis, and its activation might be enhanced after infiltration of micro-organisms[74,75]. This effect could also be demonstrated by Mommsen *et al*[30]. Jastrow *et al*[32] determined a predictive value for several cytokines, among which IP-10, MIP-1β and eotaxin appear to be most accurate. More research has to be done before the value of these cytokines can be reviewed.

Limitations

The principal limitation in this study was the heterogeneity across studies in terms of patient population, study design and statistical techniques used. Hence, meta-analysis of presented data could not be performed. Further, variations between patients in an individual study can result from differences in injury severity or injury pattern, diverse individual immunologic responses (gene polymorphisms), and general confounders such as age, sex, pre-existing diseases, number and amount of administrated therapeutic agents and secondary surgery. These aspects were not clearly outlined in most of the included studies. All these factors may alter the individual inflammatory response, and contribute to a low correlation between investigated cytokine and certain complication. Further, only a small amount of studies for each biomarker-complication combination was selected, due to the very specific research question. This made it difficult to draw clear conclusions from presented results. Also, some studies reported predictive values for the ratio of different cytokines. According to these studies, complications could be predicted more accurately when combining several cytokines in one prediction model. However, we could not include these findings in our results because of the small amount of studies investigating these specific ratios. Additionally, systemic concentrations of cytokines not necessarily reflect concentrations in end-organs. It might therefore be well possible that local concentrations of cytokines can more accurately predict the development of complications. Despite these concerns, the results presented in this review can be useful in the clinical appraisal of critically ill patients. For future studies on cytokines and polytrauma patients, we recommend the development of specific polytrauma protocols. Implementation of such protocols provides the possibility for meta-analysis in the future, as previously mentioned confounding factors would then be handled similarly. Important confounding factors that most studies did not elaborate on, include amount of resuscitation fluids administered, length of mechanical ventilation, need for nutritional support and secondary surgery. Monitoring cytokine secretion patterns without considering these factors, would give an unrealistic representation of posttraumatic immune alterations. Therefore, more research is needed to better understand the specific role of these factors in the individual immune response to trauma.

In conclusion, this article provides an overview of the results from literature concerning posttraumatic immune alterations leading to various complications and death. According to the current review, cytokine secretion patterns are different for patients developing complications, compared to patients with an uneventful posttraumatic course. Some of these cytokines, such as IL-6, IL-8 and IL-10, seem to be of value in the prediction of secondary deleterious effects after trauma. Close monitoring of these cytokines could direct physicians to the appropriate therapy of "high risk" patients, thereby reducing morbidity and mortality after polytrauma.

COMMENTS

Background

Severe trauma represents the most frequent cause of death in people below the age of 45. Early identification of patients at risk for developing complications is one of the most challenging problems in the treatment of multiple injuries. Close monitoring of cytokine secretion patterns may provide physicians with an impression of the patients' risk for developing complications. Further, cytokine secretion patterns may pose an indication for the appropriate prophylactic treatment, as well as optimal timing of surgical interventions, thereby reducing the risk of sepsis and multiorgan failure. The aim of the current review was: (1) to summarize the available knowledge on specific cytokines that are involved in the posttraumatic immune alterations; and (2) to assess the value of cytokines for predicting the development of acute respiratory distress syndrome, sepsis, muli-organ dysfunction syndrome, multi-organ failure and mortality.

Research frontiers

Polytraumatized patients that survive the initial impact of trauma, are confronted with an enormous host defence reaction, which is associated with morbidity and mortality. Over the past 20-25 years, cytokines have gained attention in the understanding of the posttraumatic pathophysiological immune alterations. Cytokines play a pivotal role in the pro- and anti-inflammatory reaction to trauma, and are essential in the subsequent defence and repair mechanisms. As cytokines serve as messenger molecules in cell-to-cell communication, they are likely to play an important role in the development of posttraumatic complications such as sepsis and multi organ failure.

Innovations and breakthroughs

Previous studies have acknowledged the correlation between cytokine concentrations and patients' clinical condition after polytrauma. Yet, specific predictors for the development of posttraumatic complications have not been identified. The available literature concerning the relation between cytokine concentrations and development of posttraumatic complications was systematically reviewed by the authors, and the data were extracted using a standardized collection tool.

Applications

This review suggests that interleukin (IL)-6, IL-8 and IL-10 are of value in the prediction of secondary deleterious effects after trauma. Close monitoring of these cytokines could direct physicians to the appropriate therapy of "high risk" patients, thereby reducing morbidity and mortality after polytrauma.

Terminology

SIRS: Systemic inflammatory response syndrome, defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference 1992; ARDS: Acute respiratory distress syndrome, determined in concordance with the American-European Consensus Conference 1994 definitions; Sepsis: Diagnosed when SIRS occurs in combination with a septic focus or positive blood culture; MODS and MOF: Multi-organ dysfunction syndrome/multi-organ failure, diagnosed based on different scoring systems.

Peer-review

This is an excellent literature analysis on an important issue. The paper was very well-structured and written.

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