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ORIGINAL ARTICLE

Soluble intercellular adhesion molecule (ICAM)-1 detects invasive fungal infections in patients following liver transplantation

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ABSTRACT

Purpose: Despite antifungal prophylaxis, liver transplanted patients are endangered by invasive fungal infections (IFI). Routinely used microbiological procedures are hallmarked by significant weaknesses, which may lead to a delay in antifungal treatment.

Methods: Culture-based fungal findings, routinely used biomarkers of infection/inflammation (e.g., procalcitonin or C-reactive protein), as well as corresponding plasma concentrations of soluble Intercellular Adhesion Molecule (ICAM)-1 were analysed in 93 patients during a period of 28 days following liver transplantation (LTX).

Results: Plasmatic sICAM-1 was significantly elevated in patients affected by an IFI within the first 28 days in comparison to fungally colonised or unobtrusive LTX patients. sICAM-1 might therefore be helpful for the identification of IFI patients after LTX (e.g., Receiver Operating Characteristic (ROC)-Area Under the Curve (AUC): 0.714 at 14d after LTX). The diagnostic performance of sICAM-1 was further improved by its combined use with different other IFI biomarkers (e.g., midregional proadrenomedullin).

Conclusion: The diagnostic deficiencies of routinely used microbiological procedures for IFI detection in patients after LTX may be reduced by plasmatic sICAM-1 measurements.

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KEYWORDS
Candida spp.; Aspergillus spp.; soluble intercellular adhesion molecule-1; invasive fungal infection; liver transplantation; fungal colonisation

Introduction

In patients with an end-stage liver disease (ESLD), liver transplantation (LTX) is nowadays a routinely used therapeutic procedure. The outcome of patients following LTX has improved within the last years due to improvements in medical care and especially by the use of an enhanced immunosuppressive treatment regimen (Trunecka 2013). However, this comes along with an increased risk for opportunistic infections, such as invasive fungal infections (IFI) (Singh 2003, Reed *et al*. 2007), which are in turn associated with a significantly increased mortality risk (Singh 2003, Neofytos *et al*. 2010). Depending on the causing pathogen, the attributable mortality of an IFI is in the range from 10 to 67% in the case of *Candida* spp. (Fortun *et al*. 2003, Husain *et al*. 2003, Shah *et al*. 2005, Eschenauer *et al*. 2015) and increases up to 80% in the case of invasive aspergillosis (IA) (Barchiesi *et al*. 2015, Nagao *et al*. 2016). In daily care, the clinician is confronted with several problems with regard to the detection of an IFI in the post-LTX time period. Culture-based diagnostic methods represent the gold standard, but are linked with significant deficiencies. E.g. blood cultures frequently show negative results even in manifest IFI cases (Clancy and Nguyen 2013, Silveira et al. 2013). Therefore, in patients presenting lasting leucocytosis or unclear fever in spite of broad-spectrum antibiotic therapy, an IFI should be taken into account. A high amount of fungal isolates at unsterile body sites or in surgical or interventional drainages may also lead to the suspicion of an IFI, which is mostly caused by *Candida albicans* or *Candida glabrata* (Vazquez *et al*. 2013). An IFI due to *Aspergillus* spp. is much more difficult to detect, since the diagnostic approach is a multimodal one, including cultures, cytology, pathology of infected tissues or fluids, as well as radiological imaging methods and

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Supplemental data for this article can be accessed here.

additional biomarker measurements (De Pauw et al. 2008, Singh et al. 2013, Patterson *et al*. 2016). These diagnostic approaches are time consuming and may cause a delayed initiation of an antifungal therapy. Alternative diagnostic methods such as Next-Generations Sequencing (NGS)-based procedures have shown to be an innovative method for the diagnosis of an IFI in LTX patients (Decker *et al*. 2019), but have not been implemented in daily clinical routine yet. Moreover, plasmatic measurements of ß-D-glucan (BDG) or galactomannan (GM) for IFI detection are restricted due to false-negative or false-positive test results (Pfeiffer *et al*. 2006, Leeflang *et al*. 2015, Singh *et al*. 2015, Decker *et al*. 2019). For the prevention of an IFI following LTX, patients most frequently receive an antifungal prophylaxis (Ljungman 2001, Slifkin *et al*. 2004). However, apart from relevant side effects, an antifungal prophylaxis may not be effective in some cases (Fortun *et al*. 2016, Giannella *et al*. 2016). In septic patients, plasma concentrations of soluble Intercellular Adhesion Molecule (sICAM)-1 were found to be a promising method for the detection of an IFI (Decker 2020). However, the diagnostic value of sICAM-1 for the detection of an IFI in patients following LTX still remains unknown.

The aims of this secondary analysis were therefore to evaluate the diagnostic performance of sICAM-1 for the identification of an IFI in comparison to fungally colonised or unobtrusive patients following LTX. Moreover, the diagnostic performance of a combined use of this new biomarker with already published IFI biomarkers (e.g., midregional proadrenomedullin) or standard infection/inflammation biomarkers (e.g., procalcitonin (PCT), C-reactive protein (CRP)) was evaluated.

Clinical significance

- Invasive fungal infections (IFI) represent a highly relevant clinical problem in liver transplanted patients, especially since culture-based diagnostic procedures are associated with a delayed initiation of an antifungal treatment due to methodical weaknesses.
- The presented study represents a secondary analysis, investigating the suitability of plasmatic soluble Intercellular Adhesion Molecule (ICAM)-1 as indicator of an IFI in patients following LTX.
- Plasmatic sICAM-1 was shown to be promising for IFI detection in patients following LTX.
- Combined measurements of midregional proadrenomedullin (MR-proADM) and sICAM-1 further increased the diagnostic performance for IFI detection

Materials and methods

Study design

Data and plasma samples were obtained from an already published observational clinical study (Decker *et al*. 2019). The study took place in the surgical intensive care unit of the Heidelberg University Hospital in the years 2014 – 2016, after approval by the local ethics committee (Ethics Committee of the Medical Faculty of Heidelberg, Trial Code No. S-098/2013/German Clinical Trials Register: DRKS00005480) All included patients gave written informed consent. Furthermore, the study was performed in accordance with the Helsinki declaration from 1964. ESLD patients ($n = 93$) undergoing orthotopic LTX were included in the study and received routine treatment according to the Heidelberg Manual for LTX (Heidelberg University Hospital 2006). Plasmatic biomarker measurements were performed at 7 timepoints (d0, d1, d2, d7, d14, d21, d28) within the first 28 days following LTX as described in (Decker *et al*. 2019). The study is reported according to the recommendations of the STROBE statement (Supplemental Material 1). The corresponding flow diagram is presented in Figure 1.

Group definitions

Fungal group classification was performed as described in (Decker *et al*. 2017, Decker *et al*. 2019). Besides positive blood cultures, fungal findings at sterile body sites, in sterile intraoperative swabs, as well as *Aspergillus* spp. in lower respiratory tract secretions in combination with pulmonary infiltrates in radiological diagnostics were classified as IFI. All other fungal findings were classified as colonisation.

Mass spectrometry

Following a previously published protocol (Incamps *et al*. 2018, Decker 2020), 520 plasma samples from 93 patients following LTX and pooled Quality samples from 48 healthy individuals were measured using mass spectrometry.

Statistical analyses

Statistical analyses on the ratio calculated after mass spectrometry analyses were performed as described elsewhere (Decker *et al*. 2017, Decker 2020). All data were collected using an electronic database (Excel 2019 Microsoft Corp, Redmond, USA) and analysed with SPSS software (Version 24.0; SPSS, Inc., Chicago, USA). JUMP 13.1.0 software (SAS Institute, Cary, USA) was used to perform Principal Component Analysis (PCA). GraphPad Prism 8.3 (GraphPad Software, La Jolla, USA), SPSS software (Version 24.0; SPSS, Inc., Chicago, USA) and PowerPoint 2019 (Microsoft Corp, Redmond, USA) were used to draw the figures. Mass spectrometry data are given as ratios without any units according to an already published protocol (Decker 2020). In brief, raw data measured on a triple quadrupole mass spectrometer were imported to Skyline software for data analysis. The ratio between endogenous transformation and internal standard transformation was calculated by summing up the detections and used as an arbitrary unit (Arb unit) for further analysis. Due to non-normally distributed data, as assessed by the Kolmogorov-Smirnov test, biomarker measurements were evaluated using a Mann-Whitney U-Test. Receiver-Operator Curve (ROC)-analysis was used to evaluate the diagnostic performance of single biomarkers, whereas a

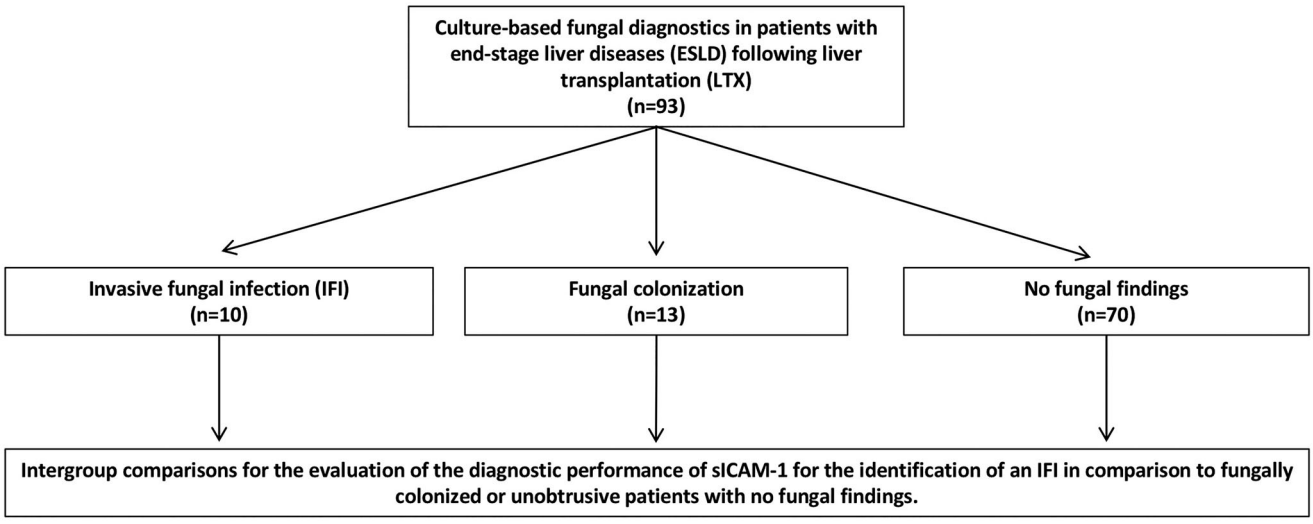

Figure 1. Flow diagram of included patients. ESLD: end-stage liver disease; LTX: liver transplantation; IFI: invasive fungal infection.

logistic regression model was used for biomarker combinations. A p-value < 0.05 was considered statistically significant. The following symbols were used to describe significance: $p < 0.05$: *, $p < 0.01$: **, $p < 0.001$: ***.

Results

Patients' characteristics and microbiological data

Ninety-three patients following LTX were reanalysed. Patients' characteristics as well as detailed information on their clinical course have already been described elsewhere (Decker *et al*. 2019) and are presented in detail in Supplemental Material 1. In total, 10 patients presented with an IFI (10.7%/candidemia: $n = 2$; invasive aspergillosis (IA): $n = 7$; mucor mycosis: $n = 1$), whereas 13 patients (13.9%) were fungally colonised (Figure 1). Patients with an IFI following LTX were characterised by a longer intensive care unit stay, a prolonged need for mechanical ventilation and a significantly reduced 28-day and 90-day survival as compared to LTX patients without an IFI.

Plasmatic sICAM-1 as an additional diagnostic tool for the diagnosis of an IFI after LTX

In IFI patients, plasmatic sICAM-1 was significantly elevated in comparison with uninfected patients starting from day 14 after LTX (Figure 2A), whereas no relevant difference could be observed within the first 7 days. ROC-analyses showed an auspicious performance of sICAM-1 for IFI detection in patients following LTX at 14d after LTX and 21d after LTX (Figure 2B). These findings are in line with the fact that IFI onset most frequently occurred at the earliest one week after LTX or at later stages. Adjusted to the timepoints of the first fungal pathogen detection, sICAM-1-levels already tended to be elevated in patients with an IFI in comparison to fungally colonised patients and revealed a significant difference at later stages (Figure 3A). Accordingly, ROC-analyses showed an AUC of 0.708 (Sensitivity 0.5, Specificity 1.0) for plasmatic sICAM-1 at the timepoint of IFI diagnosis (Figure 3B). Plasma levels of sICAM-1 did not differ significantly between IFI subgroups (e.g., candidemia, IA, mucor mycosis).

Biomarker combinations for IFI detection following LTX

By using a logistic regression model, the combination of sICAM-1 with different other IFI or infectious disease biomarkers was evaluated for IFI detection following LTX (Table 1). Especially the combination of sICAM-1 with MR-proADM, representing another innovative fungal biomarker, revealed the most promising results (Figure 4).

Discussion

Within this secondary analysis of a prospective clinical investigation in patients following LTX, sICAM-1 was shown to be suitable for the diagnosis of an IFI in patients following LTX. The diagnostic value could be further strengthened by its combined use with MR-proADM (which has previously been reported to be of diagnostic value for the detection of an IFI in liver transplanted patients (Decker *et al*. 2019)).

Patients after LTX are endangered by the occurrence of an IFI, which is particularly promoted by the intake of immunosuppressive drugs (Morris 2004, Sayegh and Carpenter 2004). The appearance of an IFI in this patient cohort is associated with a reduced long-term-survival (Sganga *et al*. 2014, Kaltenborn *et al*. 2015, Decker *et al*. 2019). Therefore, an early and reliable diagnosis is of crucial importance. Nevertheless, culture-based diagnostics are characterised by significant deficiencies (Cornely et al. 2012). Due to a rapid clearance of fungal pathogens form the bloodstream and challenging cultivation conditions, positive blood cultures can only be detected in 60-80%, especially in cases of gastrointestinal translocations (Clancy and Nguyen 2013, Silveira et al. 2013). Molecular approaches might represent a way out of this dilemma. However, PCR-based diagnostic approaches revealed a limited power for discriminating fungal colonizations, contaminations and IFIs (Avni *et al*. 2011, Patterson *et al*. 2016). In contrast, a NGS-based diagnostic

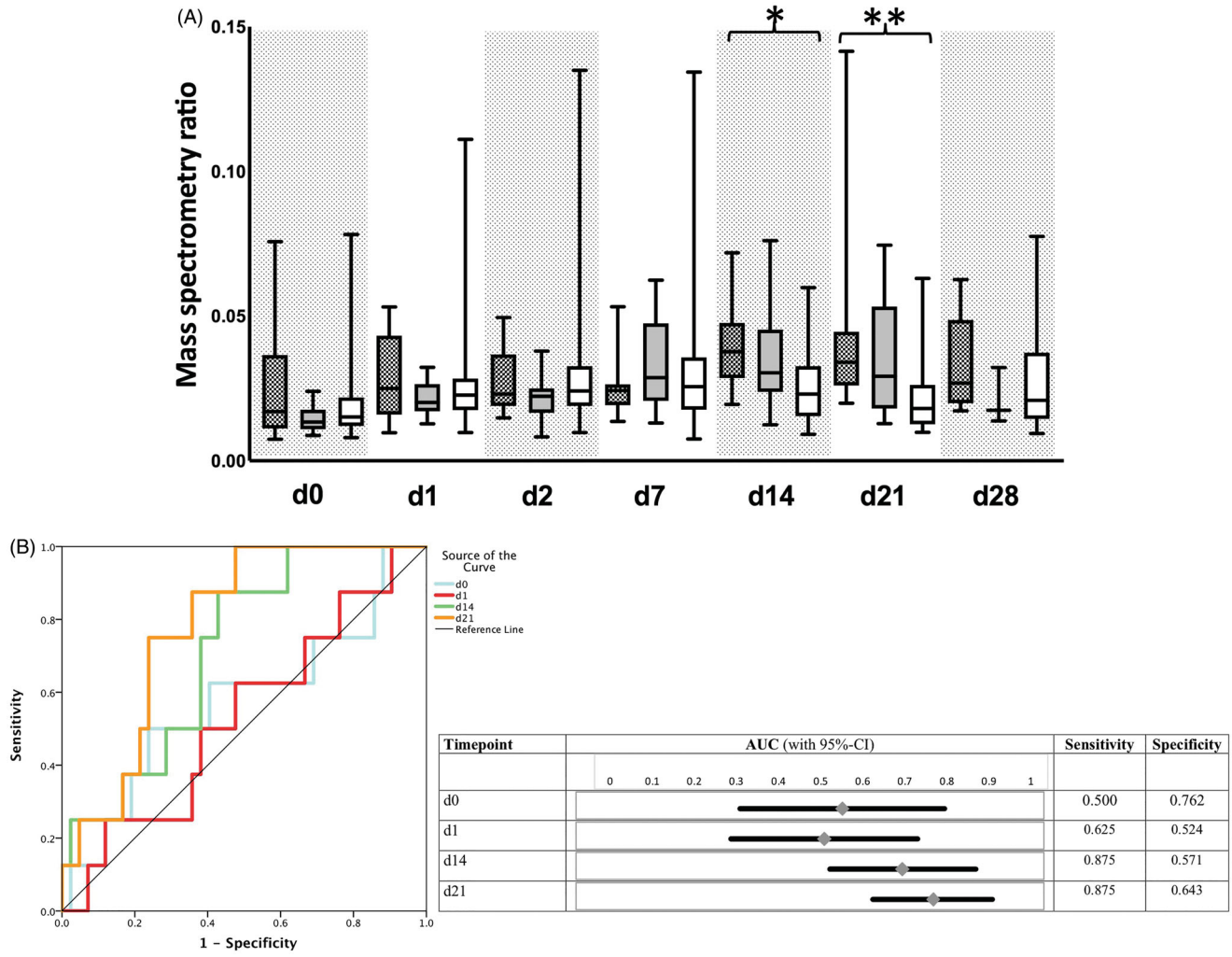

Figure 2. sICAM-1 for IFI diagnosis after LTX. (A) Plasmatic sICAM-1 was analysed in patients after LTX with an invasive fungal infection (IFI, medium grey squared box), a fungal colonisation (light grey box) or without any fungal findings (white box). Plasma samples were collected at seven predefined timepoints within 28 days following LTX. Data in box plots are presented as median, 25th and 75th percentile, with the 10th as well as 90th percentile at the end of the whiskers. Concerning symbols and higher orders of significance: $^{*}p < 0.05$, $^{**}p < 0.01$. (B) Receiver operating characteristic (ROC) analysis with sICAM-1 directly after LTX (d0), and 1 day (d1), 14 days (d14), as well as 21 days (d21) afterwards. Within this analysis, patients with an IFI were compared to both, patients with a fungal colonisation and patients without any fungal isolates, serving as controls. AUC: area under the curve; CI; confidence interval.

approach has overcome the aforementioned weaknesses of PCR-based techniques (Decker *et al*. 2019). Unfortunately, NGS-based diagnostics are still restricted to investigational settings and have not been implemented into clinical routine yet. Therefore, IFI decision making in daily clinical routine is still based on suboptimal culture-based diagnostic approaches, unspecific clinical symptoms and delayed radiologic findings.

The use of plasmatic biomarker measurements in addition to standard of care diagnostic procedures may help to facilitate IFI detection in LTX patients. However, currently available IFI biomarkers such as BDG or GM are also far from perfect. Their diagnostic value for IFI diagnosis in neutropenic patients has already been shown. Nevertheless, they are characterised by a low specificity as well as a high rate of false-positive results in patients following LTX (Pfeiffer *et al*. 2006, Leeflang *et al*. 2015, Singh *et al*. 2015). Therefore, both biomarkers are currently not recommended by the Infectious Disease Society of America (IDSA) to be used for the detection of an IFI in liver transplanted patients (Patterson *et al*. 2016).

Within a septic cohort of patients, plasmatic sICAM-1 was shown to be suitable for the detection of an IFI (Decker 2020). As indicated by the here presented work, this also seems to hold true for IFI patients following LTX. ICAM-1 represents a 58kDA single-chain protein, which is predominantly expressed on the cell surface of immune cells (e.g., B-lymphocytes) (Ley *et al*. 2007). Since ICAM-1 plays an important role in antifungal immunity, plasma levels of sICAM1 were shown to be elevated in fungal infections with *A. fumigatus* or *C. albicans* (Kidane *et al*. 2013). An inhibition of ICAM-1 leads to a decreased liberation of Interleukin-8, which evokes proinflammatory effects in infections caused by fungi (Borger *et al*. 1999, Mostefaoui *et al*. 2004, Egusa *et al*. 2005). After being cleaved from the cell surface, a soluble isoform entitled sICAM-1 is secreted into several body fluids, including blood plasma (Champagne *et al*. 1998, Lyons and Benveniste 1998). Accordingly, plasmatic sICAM-1 was elevated in patients with an IFI in comparison to fungally colonised or unobtrusive patients within the first 28 days following LTX, significantly facilitating the differentiation between fungally infected and colonised patients. Therefore, sICAM-1 might

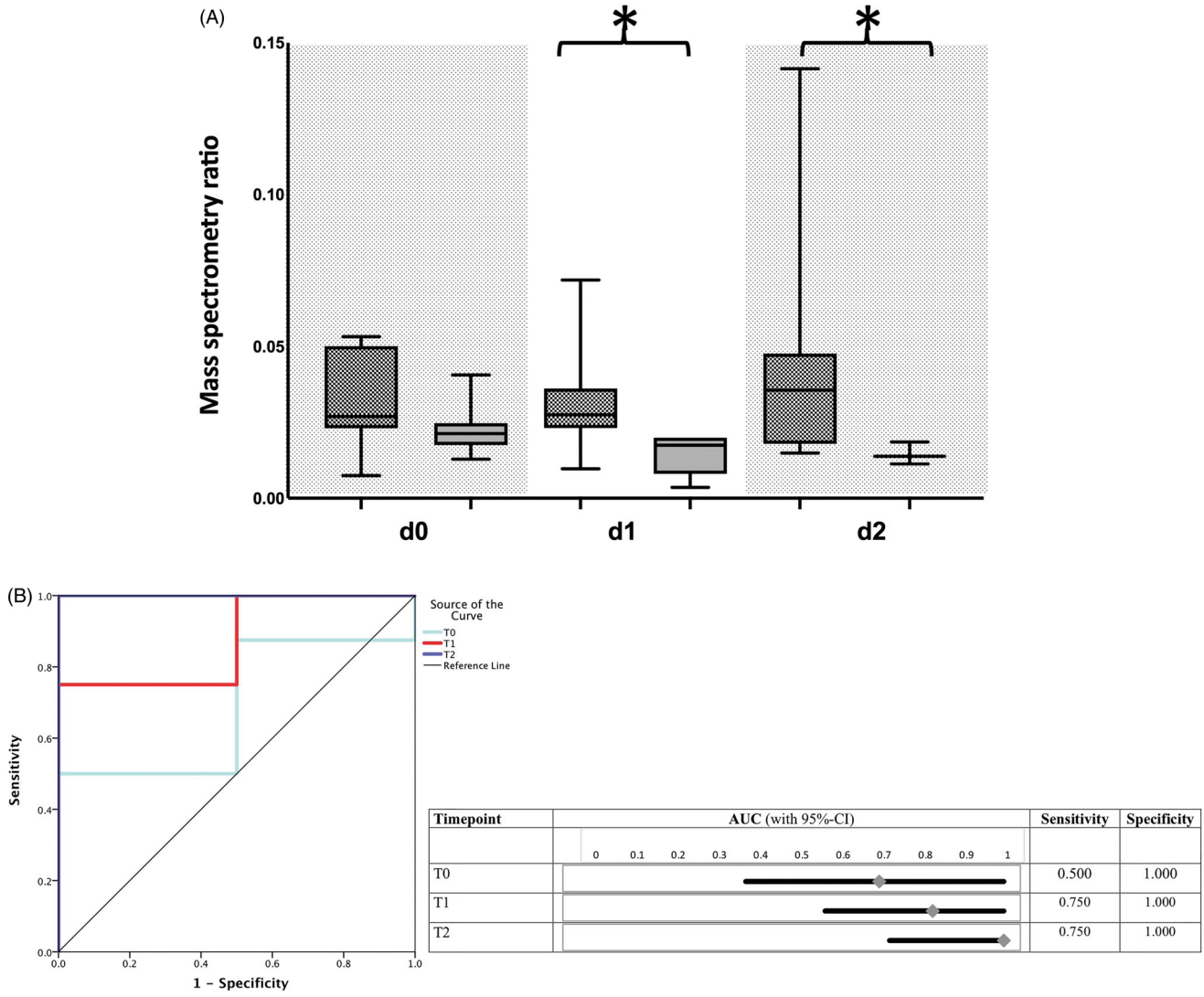

Figure 3. sICAM-1 at the timepoint of first detection of fungal isolates in patients with an IFI or a fungal colonisation after LTX. (A) Plasmatic sICAM-1 was analysed in patients after LTX with an invasive fungal infection (IFI, medium grey squared box) or a fungal colonisation (light grey box). In both groups, plasmatic sICAM-1 levels are shown for the timepoint of first detection of fungal isolates in microbiological samples (T0) and the following two timepoints (T1, T2). Data in box plots are presented as median, 25th and 75th percentile, with the 10th as well as 90th percentile at the end of the whiskers. Concerning symbols and higher orders of significance: $^{*}p < 0.05$, $^{**}p < 0.01$. (B) Receiver operating characteristic (ROC) analyses for sICAM-1 in patients with an IFI compared to colonised patients at timepoint of the first detection of fungal isolates and the following two timepoints. AUC: area under the curve; CI: confidence interval.

support clinicians in decision making, especially in those cases where routinely used diagnostic tools fail. Apart from fungal pathologies, one must keep in mind that sICAM-1 was also shown to be important in other diseases such as human sepsis, autoimmune diseases and cancer (Witkowska and Borawska 2004, Xing *et al*. 2012, Zonneveld *et al*. 2014). However, there were no differences between LTX patients with and without sepsis, autoimmune diseases or cancer; thus, these factors seem to have a limited impact in LTX patients.

Instead of using single biomarker measurements, the use of a representative biomarker panel might be of invincible diagnostic value for IFI detection. Within this context, the combination of routine infection markers (e.g., PCT, CRP) with novel fungal biomarkers (e.g., MR-proADM, sICAM-1, IL-17A) leads to an enhanced diagnostic performance for IFI diagnosis after LTX. Especially the combination of sICAM-1 with MR-proADM was shown to be most promising. The vasodilatory peptide hormone Adrenomedullin (ADM) consists of 52 amino acids, which is detected in many diseases such as infectious diseases including sepsis, but also in organ failures like kidney failure, pulmonary failure or heart failure (Valenzuela-Sanchez *et al*. 2016). During the synthesis process, ADM is derived in a 1:1 ratio together with MR-proADM, whose detailed functions are still unknown (Valenzuela-Sanchez *et al*. 2016). MR-proADM helps to discriminate critically ill patients with sepsis form those without an infectious origin (Angeletti *et al*. 2013). Moreover, MR-proADM seems to be of value for IFI diagnosis in septic patients as wells as in patients following LTX (Decker *et al*. 2017, Decker *et al*. 2019).

Limitations

The work presented here represents a secondary analysis of an already published observational single-centre study, which is characterised by a limited number of highly

Table 1. Receiver Operator Characteristic (ROC)-analyses for different biomarker combinations.

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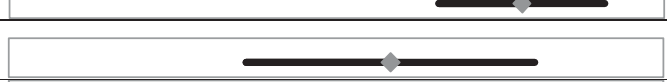
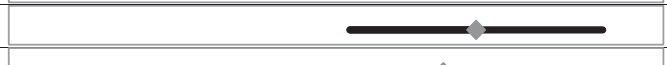
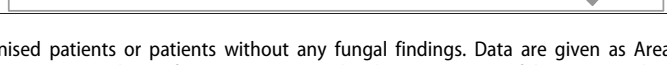
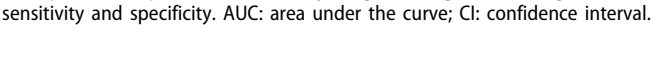
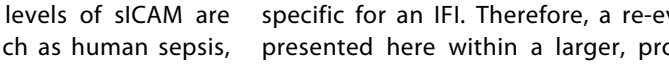
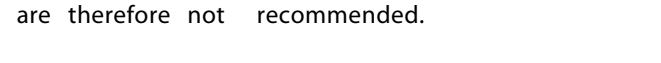
Biomarker	Timepoint	AUC (with 95%-CI)	Sensitivity	Specificity
		0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1		
CRP & sICAM-1	T0		0.500	0.756
	T1		0.375	0.805
	T2		0.625	0.610
	T3		0.375	0.976
	T4		0.750	0.829
	T5		1.000	0.561
PCT & sICAM1	T0		1.000	0.436
	T1		1.000	0.282
	T2		0.875	0.538
	T3		0.875	0.641
	T4		1.000	0.513
	T5		1.000	0.538
sICAM-1 & IL-17A	T0		0.625	0.667
	T1		1.000	0.410
	T2		0.875	0.590
	T3		0.750	0.744
	T4		1.000	0.359
	T5		1.000	0.513
sICAM-1, MR-proADM & IL-17A	T0		0.714	0.861
	T1		0.429	1.000
	T2		1.000	0.583
	T3		0.857	0.889
	T4		0.714	0.972
	T5		0.857	0.917
IL-17A, sICAM-1, MR-proADM & PCT	T0		0.714	0.861
	T1		0,429	1.000
	T2		1.000	0.583
	T3		0.857	0.889
	T4		0.714	0.972
	T5		0.857	0.944

ROC-analyses for fungally infected vs. fungally colonised patients or patients without any fungal findings. Data are given as Area Under the Curves (AUC) with 95%-confidence intervals (CI) or absolute values for sensitivity and specificity. AUC: area under the curve; CI: confidence interval.

selected patients. Moreover, elevated levels of sICAM are described for several disease states, such as human sepsis, autoimmune diseases or cancer, and are therefore not specific for an IFI. Therefore, a re-evaluation of the results presented here within a larger, prospective trial must be recommended.

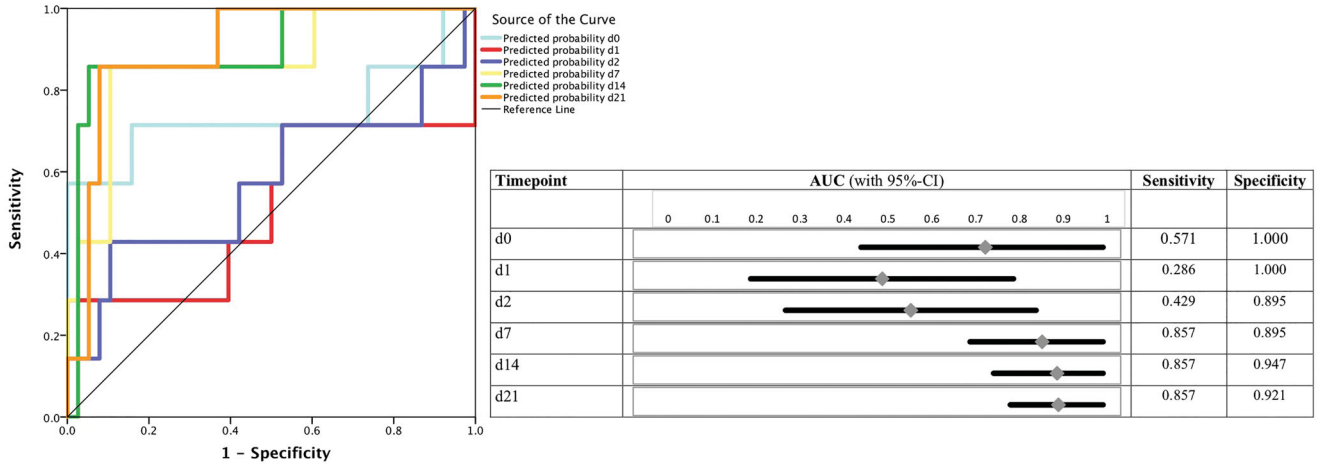


Figure 4. The combined use sICAM-1 and MR-proADM for IFI diagnosis in patients after liver transplantation (LTX). Receiver operating characteristic (ROC) analysis with sICAM-1 and MR-proADM after LTX for the timepoints (d0), 1 day (d1), 2 day (d2), 7 day (d7), 14 day (d14) and 21 day (d21) afterwards. Within this analysis, patients with an IFI were compared to both, patients with a fungal colonisation and patients without any fungal isolates, serving as controls. AUC: area under the curve; CI: confidence interval.

Conclusions

The occurrence of an IFI following LTX is associated with an increased morbidity as well as mortality. Therefore, reliable and early IFI diagnosis is of crucial importance for LTX patients. Plasmatic measurements of sICAM-1 were shown to facilitate early detection of patients at increased risk for an IFI following LTX. Moreover, sICAM-1 can overcome the diagnostic dilemma to differentiate between fungal infections and colonizations in LTX patients. The performance can be further improved by the combination of sICAM-1 with MR-proADM. This may help clinicians to guide an earlier antifungal treatment in liver transplanted patients, where routinely used procedures (e.g., microbiological cultures) for the diagnosis of an IFI fail.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Raw data were collected at Heidelberg University Hospital. Derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

SOD designed the primary study as well as the secondary analyses and wrote the manuscript. Moreover, he supported data acquisition and created the tables and figures. AI performed mass spectrometry measurements and revised the manuscript critically. HW was responsible for data acquisition and helped to revise the manuscript critically. FU, AH, AM, MM, KH and MAW were involved in the design of the primary study and the secondary analyses as well as in critical revision of the manuscript. TBru supported study design and performed all statistical analyses. Moreover, he revised the manuscript critically. SZ provided microbiological analyses and revised the manuscript critically. TBre supported the design of the primary study as well as the secondary analyses. Moreover, he coordinated manuscript drawing and revised it critically. All authors read and approved the final manuscript.

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