

Semmelweis University
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**PROGNOSTIC FACTORS OF LIVER INJURY IN ABDOMINAL TRAUMA:
IS TRANSPLANTATION A VALUABLE OPTION?**

Ph.D. thesis
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INTRODUCTION

Organ shortage situation in Eurotransplant regions/Germany

An organ transplant is currently the treatment method of choice for a large number of patients with chronic or acute organ failure. However, the shortage of suitable donor organs poses a considerable problem for transplantation medicine not only in Germany. The figure of 3,897 available postmortal donated organs in 2009 currently contrasts with the needs of approximately 12,000 patients waiting for a suitable donor organ. At the same time, the entries on transplant waiting lists have increased by about 45% in the last 17 years; this upward trend is expected to continue. As a result, the shortage of suitable donor organs means that in Germany more than 1,000 patients on the transplant waiting list die every year. According to the German Organ transplant Foundation (DSO), three times as many people are waiting for a kidney transplant than the number of organs that can be procured. As a result, on average 3 people on the waiting list die every day because no suitable donor organ is available in time.

Liver transplantation as a valuable option due to trauma

The isolated trauma of the liver are a rare event in blunt injuries of severely injured patients; yet liver injuries probably lead to a clear increase in post-trauma mortality due to the complex functioning of this organ. The immunological changes caused by blunt liver trauma are just as difficult to classify as the specific mortality. As the liver injury increases in severity, other organ systems become involved, so that total mortality results from the cumulation of all damaged organs. However, there are definitive indications leading to speculation that liver involvement superproportionally increases total mortality. The mortality rate after liver trauma documented in the literature has a wide spread and ranges between 7 and 36%. This is differentiated between early mortality, mainly due to blood loss, and late mortality. Late mortality is frequently based on secondary complications from intensive medical treatment in connection with immunological failure after a trauma which can cause sepsis/SIRS and multi-organ failure. The actual specific significance of liver injury for the emergency of such complications in this event is to date not yet fully understood.

The liver is crucial to the post-traumatic recovery of a severely injured patient. This is where proteins are formed, which constitute among other things components for coagulation and non-specific defense. It has a decisive effect on inflammatory processes and represents the center of the energy metabolism. Moreover, the Kupffer cells represent the largest macrophage pool in humans. The knowledge that liver damage alone negatively affects both early and late mortality may be an initial approach leading to organ-specific post-traumatic treatment.

In this context, it must be kept clearly in mind that the last two decades have seen a clear paradigm change concerning surgical treatment for liver injuries. With the introduction of computer tomography and the availability of clotting factors, conservative treatment of the liver injury became the method of choice for hemodynamically stable patients after blunt liver trauma. Different studies have shown that 71-89% of all patients with blunt liver trauma can be successfully conservatively treated. As a result, the survival rate is 85 to 94%. There is also agreement that despite all the opportunities for intensive fluid, blood and coagulation substitution, hemodynamically unstable patients must still be operated on.

Here, the management of a liver injury aims to control hemorrhage, preserve sufficient hepatic function and prevent secondary complications. If an adequate control of the bleeding cannot be achieved despite exhausting the current therapy options, the indication for liver transplant (LT) needs to be assessed critically in individual cases. These cases are extremely scarce in the clinical daily routine.

Nonetheless, LT are carried out due to acutely uncontrollable liver injuries in exceptional cases only. For this, indication is judged critically and discussed controversially due to usually existing secondary injuries, early septic complications, and poor general condition. Due to poor results, LT in these patients is occasionally described as “waste of organs”, however based on insufficient data.

Patients with subacute and chronic results of a liver injury need to be considered differently from the acute and due to their initial position very special group of

surgically uncontrollable patients with liver trauma. However, they share the fact that also the indication for transplantation for instance in patients with “shock liver” in the context of polytrauma or with induced liver failure after a longer intensive therapy need to be measured.

RESEARCH OBJECTIVES

AIM I

Investigate the significance of liver trauma and prognostic factors in severely injured patients

Based on an analysis of the trauma registry data from the German Society of Trauma Surgery (DGU) [Deutsche Gesellschaft für Unfallchirurgie] from 1993 to 2005 (n=24,711), the present study examined whether the participating liver injury in a polytraumatized patient superproportionally increases the incidence of sepsis and multi-organ failure, and whether survival after polytrauma is definitively decreased when the liver is involved.

Investigate the indication of liver transplantation for uncontrollable liver trauma

Our study was aimed to critically question the indication of LT on the basis of blunt and uncontrollable liver trauma; we therefore report our experience with 4 patients who all underwent LT due to accident-caused uncontrollable acute liver trauma at our center along with a comparison and discussion of our results based on the current literature.

AIM II

Try to answer the question – Is transplantation a valuable option or just a “waste of organs” in polytraumatized patients with liver injury –

Find new approaches of organ donation improvement

MATERIAL AND METHODS

First of all, with regard to the methodology of this work it should be pointed out that in order to respond to the self-declared question posed by this work, various databases and registers, which are listed in detail in the following, were used for analysis.

Prognostic factors of liver injury in polytraumatic patients

Based on an analysis of the trauma registry data from the DGU from 1993 to 2005 (n=24,711), the present analyses examined whether the participating liver injury in a polytraumatized patient superproportionally increases the incidence of sepsis and multi-organ failure, and whether survival after polytrauma is definitively decreased when the liver is involved.

It is a standardized and anonymized documentation of severely injured patients at defined phases from time point of accident to hospital discharge. In this analysis the following eligibility criteria were used:

1. Injury Severity Score (ISS) ≥ 16
2. direct admission from scene to a trauma center
3. no isolated head injury

Injury severity score (ISS) and the severity of individual injuries were determined with the 1998 revision of the Abbreviated Injury Scale (AIS). The existence of sepsis was defined based on the criteria of Bone et al. The definition of organ failure followed the SOFA score (Sequential Organ Failure Assessment). An individual organ failure was defined by at least 3 SOFA score points; a multi-organ failure (MOF) was defined as simultaneous failure of at least two organs.

All those patients with a documented liver injury (AIS abdomen < 3 and AIS liver 2-5) were assigned to the “liver trauma” group. Patients with abdominal injuries (AIS abdomen 2-5 or AIS liver < 3) were placed in the “abdominal non-liver injury” group. All remaining patients who had an AIS abdomen or liver < 3 were placed in the third “non-abdominal trauma” group (control group). The restriction to cases with ISS ≥ 16 guaranteed a minimum injury severity of AIS 3 for the primary region in the respective study groups.

Statistics (I)

From 1993 until 2001, data were collected and entered on paper sheets. Since 2002, data collection was done with internet-based data entry software with integrated plausibility checks. The anonymized data were analyzed with the statistical program SPSS (Version 14, Chicago, USA). Incidences are presented with counts and percentages, continuous values with mean and standard deviation (SD). Analysis was mainly restricted to descriptive statistics. Statistical tests were avoided due to the multiple comparisons (several groups and outcome parameters), as well as the high sample size which could lead to irrelevant significances. In selected situations only, data from the group with liver trauma were compared statistically against the remaining groups (χ^2 test for incidence rates and U-test for continuous values).

Transplantation after blunt trauma to the liver

Our study was aimed to critically question the indication of LT on the basis of blunt and uncontrollable liver trauma; we therefore report our experience with 4 patients who all underwent LT due to accident-caused uncontrollable acute liver trauma at our center along with a comparison and discussion of our results based on the current literature.

From September 1987 to December 2008, our center performed 1,529 LT (6 traumatic and 1,523 others in 4 and 1,475 patients, respectively). Apart from transplant surgery, the clinic's second major focus is on hepatobiliary surgery. In this analysis the following eligibility criteria were used:

1. patients \geq 18 years;
2. trauma-caused blunt liver injury;
3. uncontrollable clinically situation without transplantation.

The transplantations conformed to the local ethical guidelines and followed the ethical guidelines of the 1975 Declaration of Helsinki. LT was indicated in cases of uncontrollable liver injuries. It was considered contraindicated in cases of irreversible cerebral damage (i.e. slight cerebral edema is not considered a contraindication),

absence of uncontrolled extrahepatic infection (i.e. no SIRS), absence of uncontrolled multiple organ failure (MOF) (less than 3 organs including the liver).

In order to offer the best sized organ in a timely fashion, the following surgical procedures were considered for all recipients when available: deceased donor liver transplantation (DDLT) (full size and split-left lateral, left, right, extended right) and living donor liver transplantation (LDLT) (left lateral, left, right).

The conservative management of our patients consisted of: a) causal therapy, b) intense monitoring of hemodynamic, respiratory, renal, neurological, infectious, hepatic and metabolic parameters, c) minimal handling and no sedation whenever possible, d) fluid restriction but enough fluid to assure cerebral perfusion, e) hypercaloric protein-free nutrition, f) intestinal sterilization with Neomycine and Lactulose, g) fresh frozen plasma in cases of coagulation disorder. All patients received immunosuppressive induction with Prednisolone. Maintenance immunosuppression consisted of a dual therapy with calcineurin inhibitors and Prednisolone post-transplant.

We monitored the peri-operative course of each patient and noted short-term and long-term outcomes. The end of follow-up for this study was the end of July 2009.

Statistics (II)

Continuous variables are expressed as mean (\pm SD) or median (range).

RESULTS

Prognostic factors of liver injury in polytraumatic patients

The average age was 39.6 ± 19.5 years, and 72.8% were male. The average ISS was 31.9 ± 12.1 points. Patients with liver trauma were found to be younger (liver 34.9 ± 15.6 ; abdomen 37.7 ± 18.2) and more frequently female (66.0% vs. 73.5%). The number of blunt traumas was only slightly less in the liver group (91.8%) than in the non-liver abdominal trauma group (93.5%). The incidence of a primary liver injury according to the criteria mentioned was rather small, with 3.1% in the total group studied (abdomen 5.5%).

Mortality

Mortality in the liver trauma group was significantly increased (34.9%) compared to patients in the abdominal trauma group (12.0%) and patients with no primary liver or abdominal injury (control group 12.0%).

Further analysis of these differences between abdominal trauma group and the control group showed that the higher mortality in the control group is explained by the high mortality of the accompanying head injuries. Thus, a subgroup analysis shows that of the 9,574 trauma patients in the control group, 2,160 patients had suffered a relevant head injury (AIS >3). In this subgroup, mortality even reached 32.8%. The investigation of early mortality showed that 27.3% of patients in the liver trauma group died within the first 24 hours, while this rate was only 6.6% in the non-liver abdominal group.

Blood transfusion

Compared to patients with non-liver abdominal injuries, patients with severe liver trauma clearly had a greater need for blood transfusions (67.0% vs. 48.0%). The high blood loss in the liver group is correlated with the blood pressure pattern in both the preclinical and emergency room (ER) phases. Initial blood pressure was ≤ 90 mmHg preclinically in 36.4% of the liver group and 30.0% of the abdomen group. Both groups are clearly above the rate in the control group (22.0%). Blood pressure in the liver group could not be raised in any definitive way during initial clinical care (ER phase in contrast to the abdomen group (RR <90mmHg, liver: 32.2% with delta RR 4.2 mmHG; abdomen: 18.2% with delta RR: 11.2mmHG). In the ER, an initial hemoglobin content of less than 8g/dl was much more frequent in the liver group with 38.1% than in the abdomen group with 16.9% and the control group with 13.9%. Analogous to this, the average amount of transfused erythrocyte concentrate (EC) until admission to the intensive care unit was much higher in the group of patients with liver injury (8.6 units) compared to the abdomen group (4.5 units) and the control group (2.1 units).

Patients who fulfilled the criteria of a massive transfusion (number of transfused EC >10) were filtered out of the liver and abdomen groups.

Given that the average number of ECs and the average ISS in both groups of liver and abdominal trauma were almost the same (liver: 20.9 EC, ISS 39.2; abdomen 19.9 EC, ISS 38.5), the possible measured variable of an unequal EC quantity was leveled out. Thus, the high total mortality in the liver group (55.8%) compared to the abdomen group (36.5%) cannot be explained by the number of ECs. The same applies to the increased MOF (96.0% vs. 60.0%) and sepsis rate (72.0% vs. 36.0%) of the survivors.

Sepsis, Organ Failure

Compared to the other groups, increased early mortality in the liver group did not lead to a simultaneous reduction in late mortality. Patients with a liver injury showed - apart from the patients with head injuries - an average late mortality of 7.8%. One cause for the increased late mortality in comparison with patients with no liver injury is possibly the high sepsis rate (19.9%), if the first 24 hours were survived.

The increased sepsis rate in the liver group is also reflected in the frequency of organ failure (OF 48.6%) and multi-organ failure (MOF 33.3%). Compared to patients with abdominal injuries with no severe liver trauma, all three characteristics are significantly more fully developed (sepsis 11.0%, OF 33.2%, MOF 16.6%). Patients from the control group also showed a significantly decreased incidence for sepsis and multi-organ failure.

The frequency of a laparotomy is reduced from 71.6% (before 2001) to 60.4% (from 2001). Remarkably, mortality is reduced in the same period from 35.5 to 33.1%. The ISS is almost identical with 39.7 vs. 38.8.

Severity adjustment

Adjusting for severity with the RISC Score shows that patients with liver trauma die significantly more frequently than expected. The 33.0% mortality observed (95.0% confidence interval 27.6 – 38.4) offsets a prognostic mortality rate of only 23.4%. In the other two groups of injuries, prognosticated mortality hardly deviates at all from the observed mortality. These results could imply that the resuscitation and/or operative management was suboptimal. However, this is not true. Liver trauma is rather

underestimated regarding the expected prognostically impact and shows significantly worse mortality rates than in patients without liver injuries. Therefore, severe liver injury should be judged more critically with respect to mortality than the remaining abdominal injuries, with which the RISC prognosis illustrates actual mortality very well.

Transplantation after blunt trauma to the liver

Six LT were performed in 4 patients with acute liver injury (2 patients were re-transplanted). The demographics and the clinical presentation of these patients are reported individual. There were 3 men and 1 woman, ranging in age from 36 to 50 years (mean and median, 42 years and 41 years, respectively). All patients had uncontrollable liver injuries caused by motor vehicle accidents. After a median (range) follow-up of 32.95 months (10.3-55.6), 2 out of 4 patients are still alive. Half- and 4-year patient survival rates are 50% and 25% with a corresponding graft survival of 25%, respectively.

CONCLUSION

Investigate the significance of liver trauma and prognostic factors in severely injured patients

In our opinion, unstable patients should be identified by the following parameters: 1) location of the source of bleeding, i.e., free fluid in the abdomen in the initial ultrasound, if need be with an increase in the course of action; 2) volume loss, i.e., substitution is required for hemodynamic stability when systolic blood pressure falls below 80 - 90 mmHG; 3) signs of systemic hypoperfusion with negative base excess and pH and where applicable with an initial hemoglobin under 8 mg/dl with signs of consumptive coagulopathy.

Knowledge of the additional dangers documented here as they can arise from a liver injury and may possibly be positively affected by e.g. a specific coagulation treatment and an early substitution of ECs. The immunological changes to be expected from a liver injury in the meantime may possibly even reinforce the frequently described post-trauma immunosuppression.

Investigate the indication of liver transplantation for uncontrollable liver trauma

In conclusion, we largely agree with the aforementioned reports. The therapeutic option of liver transplantation also needs to be accessible for patients with liver injuries caused by trauma. However, not least due to the mentioned poor transplantation results in severely injured patients, indication for transplantation needs to be critically proposed by the attending surgeons.

Try to answer the question – Is transplantation a valuable option or just a “waste of organs” in polytraumatized patients with liver injury –

It is essential to sensibly and appropriately allocate the organs so that the shortage of donor organs is not further enlarged. In patients where no hemodynamic stabilization can be achieved despite exhaustion of all extensive care measures, transplantation should not be considered any further. Although, there is a fundamental difference regarding the timeframe after trauma during which patients are to be transplanted. It has shown, that especially patients with acute, non-controllable liver injuries as described by us have clinically changed for the worse rapidly after transplantation and have died in MOF. Therefore, we postulate that indication for transplantation in these patients may only be provided after critically reviewing every single case as not to “waste of organs”.

Identifying new approaches to improving organ donation

It should be noted that the success of transplantation medicine with a simultaneously increasing shortage of donor organs will only be assured if all available resources are exploited. Increasing acceptance of “expanded criteria donor” organs appears more justified than ever under these circumstances, but also with sustained good results despite constantly deteriorating organ quality. Approaches to increase the transplant quality, not only of extended criteria donor (ECD) organs, offer further developed possibilities that support perfusion such as machine perfusion and optimized perfusion solutions. Moreover, shortened ischemic periods are achieved through further improved logistics and allocation processes, which together with individualized, medicinal immune suppression ultimately benefit the transplant and the organ recipient. In addition to this continuously improving and thus optimized use of postmortal organs, it

must also be the common objective of the medical profession and politics to increase the overall number of donor organs and to improve their quality.

In order to achieve this, priority should be given to an improved exploitation of the existing organ donation potential through hospital-based advising, for example by a contact person for organ donation at each intensive care unit. Information and advising by Eurotransplant and the transplant centers for physicians, nursing staff and the population are of key importance here. Furthermore, to an ever great extent it will be the task of all parties involved in the field of transplantation to present organ donation, the allocation and transplantation of organs, and all the decisive aspects relating to the readiness of organ donation such as trust, safety and equity in a transparent manner. Conducting advisory discussions on the topic of organ donation with the relatives of the deceased is a special task for physicians. One measure should include involving a physician with special communicative expertise. It remains to be hoped that in this way a higher acceptance rate for organ donation will be more successfully achieved throughout all population groups in the future. In tapping into all resources and approaches for the optimized exploitation of donated postmortal organs, it should be possible to assure the medical care mandate of transplantation medicine in Germany in the future as well.

Based on previous studies, the recording of organ donors with “expanded criteria” in a targeted analysis is useful and necessary for new ways of improving organ donation. The corresponding creation of a database is currently underway at the University Hospital of Essen within the scope of a “Clinical Research Group (KFO)” sponsored by the German Research Foundation (Deutsche Forschungsgemeinschaft – DFG). Further local, national and international analyses are additionally necessary to identify the limits to expanding donor acceptance criteria.

PUBLICATIONS

Publications for the dissertation based on

1. **Heuer M**, Kaiser GM, Lendemans S, Vernadakis S, Treckmann JW, Paul A. Transplantation after blunt trauma to the liver: a valuable option or a “waste of organs”? Eur J Med Res 2010;15:169-173.

IF 1,040

2. Radünz S, Hertel S, Schmid KW, **Heuer M**, Stommel P, Frühauf NR, Saner FH, Paul A, Kaiser GM. Attitude of health care professionals to organ donation: two surveys among the staff of a german university hospital. Transplant Proc 2010;42:126-129.

IF 1,055

3. **Heuer M**, Hertel S, Wirges U, Philipp T, Gerken G, Paul A, Kaiser GM. Evaluation of organ donor card holders among public officials of a major german city. Transplant Proc 2009;41:2505-2508.

IF 1,055

4. **Heuer M**, Taeger G, Kaiser GM, Nast-Kolb D, Kühne CA, Ruchholtz S, Lefering R, Paul A, Lendemans S and The Trauma Registry of the DGU. Prognostic factors of liver injury in polytraumatic patients. Results from 895 severe abdominal trauma cases. J Gastrointestin Liver Dis 2009;18:197-203.

IF nd

5. Lendemans S, **Heuer M**, Nast-Kolb D, Kühne CA, Dammann M, Lefering R, Flohé S, Ruchholtz S, Taeger G. Bedeutung des Lebertraumas für die Inzidenz von Sepsis, Multiorganversagen und Letalität bei Schwerstverletzten. Eine organspezifische Auswertung von 24.771 Patienten des Traumaregisters der DGU. Unfallchirurg 2008;111:232-239.

IF 0,686

Other publications

I. Original articles

1. Kaiser GM, **Heuer M**, Stanjek M, Schoch B, El Hamalawi B, Waydhas C, Mummel P, Radünz S, Wirges U, Kraus H, Frühauf NR, Lütkes P, Schmid KW, Paul A. Organspendeprozess an einem Krankenhaus mit Maximalversorgung. Dtsch Med Wochenschr 2010;135:2065-2070.

2. **Heuer M**, Reinhardt R, Kneiseler G, Würzinger P, Xunfeng Z, Fan Hua, Fu Jian, Paul A, Kaiser GM. Liver transplantation in swine without veno-venous bypass. *Eur Surg Res* 2010;45:20-25.
3. Juntermanns B, Radünz S, **Heuer M**, Hertel S, Reis H, Neuhaus JP, Vernadakis S, Trarbach T, Paul A, Kaiser GM. Tumor markers as a diagnostic key for hilar cholangiocarcinoma. *Eur J Med Res* 2010;15:357-361.
4. **Heuer M**, Hussmann B, Schenck M, Nast-Kolb D, Ruchholtz S, Lefering R, Paul A, Taeger G, Lendemans S und Das TraumaRegister der DGU. Nierenverletzung und Polytrauma: Outcome, Verlauf und Behandlungsalgorithmus. Eine organspezifische Auswertung von 835 Patienten des Traumaregisters der DGU. *Unfallchirurg* 2010; in press.
5. Mathé Z, Treckmann JW, **Heuer M**, Zeiger A, Sauerland S, Witzke O, Paul A. Stented ureterovesical anastomosis in renal transplantation: Does it influence the rate of urinary tract infections? *Eur J Med Res* 2010;15:297-302.
6. Juntermanns B, Treckmann JW, Radünz S, Saner FH, Vernadakis S, Kühl H, Reis H, Paul A, **Heuer M**, Kaiser GM. Klatskin-mimicking lesions: still a diagnostical and therapeutical dilemma? *Hepatogastroenterology* 2010; in press.
7. **Heuer M**, Taeger G, Kaiser GM, Nast-Kolb D, Kühne CA, Ruchholtz S, Lefering R, Paul A, Lendemans S and The Trauma Registry of the DGU. No further incidence of sepsis after splenectomy for severe trauma: a multi-institutional experience of the German trauma registry with 1,630 patients. *Eur J Med Res* 2010;15:258-265.
8. Treckmann JW, Paul A, Sgourakis G, **Heuer M**, Wandelt M, Sotiropoulos GC. Surgical treatment of nonparasitic cysts of the liver: open versus laparoscopic treatment. *Am J Surg* 2010;199:776-781.

9. Radünz S, **Heuer M**, Hertel S, Schmid KW, Stommel P, Frühauf NR, Paul A, Kaiser GM. Organspendebereitschaft an einer Universitätsklinik – Ergebnisse einer Mitarbeiterbefragung -. *Intensivmed* 2009;46:437-440.
10. **Heuer M**, Zeiger A, Kaiser GM, Mathé Z, Goldenberg A, Sauerland S, Paul A, Treckmann JW. Use of marginal organs in kidney transplantation for marginal recipients: too close to the margins of safety? *Eur J Med Res* 2009;15:31-34.
11. Saner FH, **Heuer M**, Meyer M, Canbay A, Sotiropoulos GC, Radtke A, Treckmann JW, Beckebaum S, Dohna-Schwake C, Olde Damink SWM, Paul A. When the heart kills the liver: Acute liver failure in congestive heart failure. *Eur J Med Res* 2009;14:541-546.
12. **Heuer M**, Hertel S, Remmer N, Wirges U, Philipp T, Gerken G, Paul A, Kaiser GM. Organspendebereitschaft: Auswertung einer Umfrage zu Gesundheitsthemen. *Dtsch Med Wochenschr* 2009;134:923-926.
13. **Heuer M**, Kaiser GM, Saner FH, Erim Y, Wirges U, Paul A, Gerken G, Canbay A. Eine konsequente Aufklärung könnte die Organspendebereitschaft der türkisch-islamisch stämmigen Bevölkerung deutlich erhöhen. *Med Welt* 2009;60:87-90.
14. **Heuer M**, Benkö T, Cicinnati VR, Kaiser GM, Sotiropoulos GC, Baba HA, Paul A. Effect of low dose rapamycin on tumor growth in two human hepatocellular cancer cell lines. *Transplant Proc* 2009;41:359-365.
15. Nadalin S, **Heuer M**, Wallot M, Auth M, Schaffer R, Sotiropoulos GC, Ballauf A, van der Broek MA, Olde-Damink S, Hoyer PF, Broelsch CE, Malagò M. Paediatric acute liver failure and transplantation: the University of Essen experience. *Transpl Int* 2007;20:519-527.

II. Case reports

1. **Heuer M**, Kaiser GM, Mönninghoff C, Paul A. Retroperitoneal hematoma: vascular complication after percutaneous coronary intervention. *Int J Case Rep Images* 2010;1:15-16.
2. Vernadakis S, Adamzik M, **Heuer M**, Antoch G, Baba HA, Fiedler M, Buer J, Paul A, Kaiser GM. Hemikolektomie bei Kolonischämie: Ein Fallbericht von Schweinegrippe mit letalem Verlauf. *Chirurg* 2010;81:841-845.
3. **Heuer M**, Kaiser GM, Gauler TC, Sheu SY, Kühl H, Paul A. Pseudomyxoma peritonei bei muzinösen Zystadenokarzinomen. *chir prax* 2009;70:581-588.
4. Saner FH, **Heuer M**, Rath PM, Gensicke J, Radtke A, Drühe N, Rüngeler EM, Nadalin S, Malagò M, Broelsch CE. Successful salvage therapy with tigecycline after linezolid failure in a liver transplant recipient with MRSA pneumonia. *Liver Transpl* 2006;12:1689-1692.

III. Reviews

1. **Heuer M**, Kloke M, Henning M, Hierner R, Niebel W. Diagnostik und Therapie chronischer Wunden bei Tumorpatienten und in der Palliativmedizin. *WundM* 2009;3:108-115.
2. **Heuer M**, Frühauf NR, Treckmann J, Witzke O, Paul A, Kaiser GM. Organentnahme und Nierentransplantation aus der Sicht des Chirurgen. *Dtsch Med Wochenschr* 2009;134:412-416.
3. Nadalin S, Wallot M, Malagò M, **Heuer M**, Frühauf NR, Ballauf A, Auth M, Paul A, Valentin-Gamazo C, Lang H, Broelsch CE. Lebertransplantation im Kindesalter. *chir prax* 2006;66:115-25 und *pädiat prax* 2005;66:671-681.
4. Kaiser GM, **Heuer M**, Frühauf NR, Kühne CA, Broelsch CE. General handling and anesthesia for experimental surgery in pigs. *J Surg Res* 2006;130:73-79.

IV. Book article

1. **Heuer M**, Saner FH, Kaiser GM, Paul A. Intensivmedizinische Therapie potenziell hirntoter Spender. Eckart·Forst·Briegel – Intensivmedizin – 33. Erg.-Lfg. 4/09, XIII - 13, 1-10.

V. Letter to the editor

1. Radünz S, **Heuer M**, Trarbach T, Mathe Z, Baba HA, Paul A, Sotiropoulos GC. Long-term survival after „liver first“ approach for locally advanced rectal cancer and synchronous liver metastases. Int J Colorectal Dis 2010; in press.

VI. Published abstracts

1. Radünz S, Kirchner C, Frühauf NR, **Heuer M**, Paul A, Kaiser GM. Willingness to donate organs among medical students prior to and after a lecture about organ donation. Transpl Int 2010;23:38.
2. **Heuer M**, Treckmann JW, Canbay A, Saner FH, Kaiser GM, Paul A, Mathe Z. Nonalcoholic steatohepatitis an increasing indication for liver transplantation. Experience of the university hospital of essen. Transpl Int 2010;23:47.
3. Reinhardt R, **Heuer M**, Rauen U, Kneiseler G, Würzinger P, Paul A, Kaiser GM. Safety study of modified HTK solution – first results after liver transplantation in swine. Transpl Int 2010;23:47.
4. Vernadakis S, Sotiropoulos G, Kaiser GM, Mathe Z, **Heuer M**, Beckebaum S, Treckmann JW, Paul A. Liver transplantation for polycystic liver disease. The university of Essen experience. Transpl Int 2010;23:51.
5. Vernadakis S, Mathe Z, Sotiropoulos G, Kaiser GM, Beckebaum S, **Heuer M**, Saner FH, Treckmann JW, Paul A. Long-term outcomes after orthotopic liver transplantation in HIV-infected patients with end-stage liver disease. Transpl Int 2010;23:52.

6. Remmer N, **Heuer M**, Treckmann JW, Wirges U, Paul A, Kaiser GM. Evaluation of organ donor card holders among an employee cluster in a major German city. *Transpl Int* 2010;23:65.
7. **Heuer M**, Kaiser GM, Kühl H, Müller S, Paul A. The role of FDG-PET in evaluation of hepatocellular carcinoma after liver transplantation. *Am J Transplant* 2009;9:446.
8. **Heuer M**, Benkö T, Cicinnati VR, Sotiropoulos GC, Kaiser GM, Baba HA, Paul A. Effect of low dose rapamycin on tumor growth in two human hepatocellular cancer cell lines. *Am J Transplant* 2009;9:664.
9. **Heuer M**, Hertel S, Wirges U, Philipp T, Gerken G, Paul A, Kaiser GM. Organspendebereitschaft: Auswertung einer Umfrage zu Gesundheitsthemen. *Transplantationsmedizin* 2008;Supp.II:132.

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