Discovery of temporal structure intricacy in arterial blood pressure waveforms representing acuity of liver transplant and forecasting short term surgical outcome via unsupervised manifold learning

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Abstract

Background:
Arterial blood pressure (ABP) waveform evolves across each consecutive pulse during the liver transplant surgery. We hypothesized that the quantification of the waveform evolution reflects 1) the acuity of the recipient undergoing liver transplant and 2) the intraoperative dynamics that forecasts short-term surgical outcomes.

Methods:
In this prospective observational single cohort study on living donor liver transplant surgery, we extracted the waveform morphological evolution from the ABP data with the unsupervised manifold learning waveform analysis. Two quantitative indices, trend movement and fluctuation movement, were developed to represent the slow-varying and fast-varying dynamics respectively. We investigated the associations with the liver disease acuity represented with the Model for End-Stage Liver Disease (MELD) score and the primary outcomes, the early allograft failure (EAF), as well as the recently developed EAF scores, including the Liver Graft Assessment Following Transplantation (L-GrAFT) score, the Early Allograft Failure Simplified Estimation (EASE) score, and the Model for Early Allograft Function (MEAF) score.

Results:
Sixty recipients were enrolled. The presurgical trend movement was correlated with the MELD scores. It decreased in the anhepatic phase. The neohepatic trend movement correlated with the L-GrAFT scores, the EASE score, and the MEAF score. Regarding the constituent of the EAF scores, the trend movement most correlated with the postoperative day 7 bilirubin.
Conclusions:
The ABP waveform evolution intricacy in the presurgical phase reflects recipients’ acuity condition while that in the neohepatic phase reveal the short-term surgical outcome calculated from laboratory data in postoperative day 7-10. The waveform evolution reflects the intraoperative contribution to the early outcome.

Keywords
Arterial blood pressure waveform; liver transplant; early allograft failure; manifold learning; unsupervised learning

Introduction
Liver transplant is a lifesaving but complicated surgery. While the surgical procedure becomes mature nowadays, it is an ongoing endeavor to assess the recipient condition and surgical outcome due to the complex physiological nature involving various system interactions\(^1\);\(^2\). We incidentally observed that the arterial blood pressure (ABP) waveforms during the liver transplant surgery contain a temporal evolution phenomenon: recipients of favorable conditions possess richer intricacy in their ABP waveform morphology evolution with time, and vice versa\(^3\) (Fig. 1).

The observation of waveform evolution between each consecutive pulse is enabled by the unsupervised manifold learning technique we recently developed for cardiovascular waveform analysis\(^4\);\(^5\). By capturing subtle waveform morphological change and condensing its information as a trajectory in a multivariate coordinate, the Dynamic Diffusion Map (DDMap) technique offers 3-dimensional (3D) images for visual inspection (Fig. 1). This technique has been employed in machine learning tasks, including detecting ECG waveform for ischemic heart disease, as well as presenting the ABP waveform dynamics in vasoactive episodes and noxious stimuli\(^6\);\(^6\).

In contrast to the “one representative waveform” approach exploited in clinical
scenarios to predict hypotension, to assess arterial stiffness, or to derive the profiles of the cardiovascular system\textsuperscript{7-10}, the waveform temporal evolution is a new dynamical information among all consecutive pulses that has never been reported before our incidental findings, which inspired us to further investigate as direct ABP monitoring is mandatory during the transplant surgery.

To assess the liver disease acuity, researchers have employed laboratory data\textsuperscript{11} to develop indices, including the Child-Pugh score, the Model for End-Stage Liver Disease (MELD) score and MELD-Na score\textsuperscript{2, 12, 13} for years\textsuperscript{12, 14, 15}. The success of laboratory data combined with mathematical formula has led to the research in the prediction of the Early Allograft Failure (EAF) outcome. We have seen the development of EAF scores from the Model for Early Allograft Function (MEAF) score\textsuperscript{14-18} and the Early Allograft Failure Simplified Estimation (EASE) score\textsuperscript{19} to the recently-developed Liver Graft Assessment Following Transplantation (L-GrAFT) scores\textsuperscript{20, 21} based on the laboratory data till postoperative day (POD) 10.

However, the crucial moment is still the surgery, during which the laboratory examination inevitably falls behind the dynamical surgical progress and provides no practical information regarding the present condition. To fill the void, we proposed to exploit the temporal evolution intricacy phenomenon, which may reveal the dynamical regulatory ability to maintain homeostasis in the cardiovascular system\textsuperscript{4}.

Regarding this phenomenon, we proposed two intricacy indices, the trend movement and fluctuation movement, to quantify the temporal evolution intricacy during liver transplant surgery. We hypothesized that these indices are associated with 1) the recipient’s acuity before the transplant surgery, 2) the transitions in surgical phases from the presurgical phase to the anhepatic phase and neohepatic phase, and 3) inference of the short-term surgical outcome in terms of the EASE, MEAF, L-GrAFT\textsubscript{7} and L-GrAFT\textsubscript{10}. 
Fig. 1.

Arterial blood pressure (ABP) data and waveforms from 2 demonstration cases in presurgical phase and in anhepatic phase show 4 pulse-by-pulse trajectories (thin lines) and the trend movements (thick lines) in a 3-D image after the considered manifold learning waveform analysis. The trajectories and trends representing ABP temporal evolution in the 4 zoomed subfigures show high-dimensional (multivariate) movements indicating complex pathophysiological interactions. Fading in color indicates time direction. In the presurgical phase, case 1 (MELD score: 8) presents more fluctuation movement and trend movement than case 2 (MELD score: 32). Both movements decreased in anhepatic phase. Note that the 4 trajectories and
their trends move with multitude directions forming complex shape in 3-D space, which is a simplified representation of their multi-dimensional (multivariate) activities. (Supplementary videos at https://youtu.be/P9rlD9xpl90 and https://youtu.be/yu1rucN0S-4)

Material and Methods

Patients and methods

This is a single center prospective observational study between 2018 and 2021 in Taipei Veterans General Hospital, Taipei, Taiwan. After Institutional Review Board approval (IRB No.: 2017-12-003CC and 2020-08-005A) and written informed consent obtained from each patient included in this study, 60 living donor liver recipients (LDLR) were recruited. There were two reasons to select LDLR. First, living donors from family members outnumbered cadaveric donors in Taiwan and second, the variance in cold ischemia time of the graft was minimal. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

The latest laboratory data within one week before the elective surgery was used to calculate the MELD score, MELD-Na score and Child-Pugh score. The MELD scores were used for patients awaiting liver transplantation to predict mortality and to improve graft allocation. The original MELD score comprised 3 laboratory data, including the total bilirubin, creatinine, and international normalized ratio (INR). The revised MELD-Na score includes sodium as the fourth variable to improve its performance.

The continuous physiological waveform signal data were collected from the patient monitor (GE CARESCAPE™ B850, GE Healthcare, Chicago, IL) via the data collection software S5 Collect (GE Healthcare) from the liver transplant recipient who
underwent surgery during the whole surgical period. The physiological data, including electrocardiogram (ECG), ABP, central venous pressure (CVP) and pulse oximetry, were recorded from the start of the anesthetic maintenance through the whole surgery, but only ABP was used in the upcoming analysis. The recorded waveforms were uniformly sampled at 300 Hz. In addition, we routinely set a portocaval shunt during the anhepatic phase to release the portal flow and the congestion of the intestine. We registered the specific time points, including the hilum clamp before hepatectomy, end of the hepatectomy, portocaval shunt establishment, portal vein reperfusion, hepatic artery reperfusion, and completion of bile duct anastomosis. After the operation, the liver recipients were transferred to the Intensive care unit (ICU) where the postoperative recovery was under the discretion of physicians in ICU, who were blinded of this study.

The main clinical outcome is the graft failure determined by patient death or liver retransplantation within 3 months\(^\text{20}\). The prognostic condition following transplantation were evaluated by 4 recently developed EAF scores\(^\text{20}\), including the MEAF score\(^\text{16}\), the L-GrAFT\(_7\) and L-GrAFT\(_{10}\) scores, as well as the EASE score\(^\text{19}\). The MEAF score comprised alanine aminotransferase (ALT), the international normalized ratio (INR), and the bilirubin data. The L-GrAFT\(_7\) score and L-GrAFT\(_{10}\) score comprised the laboratory data of AST, INR, total bilirubin, and platelet counts at day 7 and day 10 respectively. In comparison with the above scores, the EASE score consumed more items, including the laboratory data of aspartate aminotransferase (AST), platelet, bilirubin within 10 days, as well as the MELD score, the number of transfused packed red blood cell during surgery, the events of vascular thrombosis within 10 days after the surgery and whether the early volume of the institution is larger than 70 cases per year. It is apparent that the bilirubin, AST, PLT and INR are the common constituents of the above EAF scores. Per institutional routine,
recipients underwent daily venous blood check within POD7. Afterward recipients of good recovery at the discretion of the surgeon would be checked for every other day. The missing data point is imputed by a linear regression method under the assumption that the laboratory information is changing individually and localized in time.

**Waveform data selection and processing**

We chose 3 surgical phases for data analysis, the presurgical phase, the anhepatic phase and the neohepatic phase. The presurgical phase data were chosen when the anesthetic maintenance started and the preparation for the imminent surgery was undergoing as it represented the baseline condition without the surgical stimulation. We chose the first 800 ABP pulses from each recipient, which amounted to less than 10 minutes of data collection period in the presurgical phase, as the representation of the recipient’s condition with the old liver. The anhepatic phase data were chosen as a 10-minute period after the portocaval shunt had been established. We inspected the waveform to ascertain neither drastic change nor severe artifact during this 10-minute period. The consideration of the constant 10-minute period approach would be more suitable for standardization for future research. The neohepatic phase data were chosen as a hemodynamically stable 10-minute period after the anastomosis of the biliary duct, and before the abdominal wound closure was performed. During this period, the reperfusion and the re-establishment of the hepatic artery flow had performed, and the new liver graft was supposed to have functioned for a while.

To prepare the consecutive ABP waveform pulses for the manifold learning (Fig. 1), we use the maximum of the systolic phase slope as the fiducial point to obtain each pulse cycle. Legitimate ABP pulses were automatically detected and extracted based
on the following criteria: the pulse width, the extreme value, the pulse pressure, the
duration between two successive pulses should be within reasonable limits, which
are determined inter-individually and dynamically. As the heart rate is time-varying,
the pulse count and the time duration are not linearly related. It is worth noting that
we chose the 800-pulse data in the presurgical phase for the uniform contribution
from each case.

**Unsupervised manifold learning and Intricacy quantification**

The pulse-by-pulse ABP waveform temporal evolution is too subtle to be directly
gauged by the naked eye. We use the unsupervised manifold learning algorithm,
DDMap, to condense the waveform information for visualization and quantification.
After the above-mentioned pre-processing procedure, we treat those consecutive
pulses as high dimensional data points and finds a geometric structure (the manifold)
in the high dimensional space representing the trajectory of the waveforms evolving
with time (Fig. 1).

The main technical innovation, in a nutshell, is measuring every waveform by all the
other waveforms as the gauges. That is, the knowledge gained from this method is
the united contribution of the waveform data, which also supports the robustness
(less susceptible to the noise). In the frame of unsupervised machine learning, this
method consumes only the successive pulse-to-pulse waveform morphology without
the input of time labeling, medical history, lab test data, or the surgical procedure.
This data-centered agnostic approach allows us to represent the waveform evolution
in a more comprehensive manner. 

While DDMap provides a concise overview of the complex dynamical evolution of
ABP waveforms, the trajectory consisting of consecutive pulses forms a unique shape
that cannot be simply measured from the raw ABP waveform (Fig. 1, Fig. S1). Our
past studies and other lines of evidence support that ABP waveforms are determined
by several factors including the vascular tone, cardiac contractility, and preload. A
simple noxious stimulus will elicit multiple reflexes producing a complex trajectory
shape in high dimensional space. Our empirical findings that the more waveform
evolution intricacy is associated with a better condition justifies the employment of the manifold learning. The main feature we observed is that the trajectory consists of a trend (slowly varying) and fluctuation (fast varying) in the high dimensional space.

We proposed two indices to quantify the intricacy; the fluctuation movement quantifies the fast-varying evolution, and the trend movement quantifies the slow-varying evolution (Fig. S1). Both indices were designed to range roughly from 0-100 based on the median value and the interquartile range (IQR) of the data in this study. More technical information is presented in the supplementary.

Validation analysis

Sensitivity analysis was performed to evaluate the effect of parameter selection. Since both indices, the trend movement and the fluctuation movement, are based on the trajectory analysis, we investigate the effect of different filtering length $K$ in ABP intricacy quantification.

To further validate our hypothesis of temporal intricacy in the ABP waveform morphology, we employed different null models. The random perturbation of the time sequence labeling was designed to validate the ABP temporal evolution intricacy; the perturbation of case labeling of the ABP waveform data was designed to validate our hypothesis between ABP waveform evolution and the liver disease acuity; the perturbation by replacing each pulse wave with each mean blood pressure value was to validate the waveform morphological information.

Statistical analysis

We explored three clinical information by the proposed intricacy indices. The first one was directly evaluating the correlation between the intricacy indices and the MELD scores in the presurgical phase. The second one was the intricacy evolution from the anhepatic phase to neohepatic phase. The rationale is that the ability to
dynamically reflect the drastic pathophysiological effect from the presurgical to the anhepatic phase should present as the variation in the correlation with the MELD scores. Third, we investigated how the intricacy indices in the neohepatic phase are associated with the EAF scores and their constituents.

Pearson correlation was used to establish the association between the intricacy indices and the clinical condition. The bootstrap resampling without replacement for statistical inference was used for exemption from the normal distribution assumption. The 95% confidence interval (CI) of each considered statistic was derived from the bootstrap resampling without replacement with 100,000 resamples. Note that a higher MELD score represents a worse acuity while we hypothesize that a higher intricacy reflects better homeostasis of the human body, so the ideal correlation coefficient is -1. It is the same case with any other quantity representing the worse condition with a higher value. The association of indices with other scores or factors was further evaluated with multivariate regression, where the relative importance of each factor is derived from the R square. The demographic data and laboratory data were expressed as median (1st quartile, 3rd quartile and interquartile range (IQR)). Statistical results are expressed as mean and its 95% CI. Null hypothesis test was considered significant when the P value < 0.05.

We performed the waveform data processing and manifold learning with C# language (Visual Studio community 2019, Microsoft, Redmond, WA), and the statistical analyses with R (version 4.1.0; the R Foundation for Statistical Computing). The calculation of MELD, MELD-Na, and EAF scores were performed with spreadsheet software Excel (Microsoft, Redmond, WA), where each formula was sourced from each corresponding author. MELD and MELD-Na were calculated without rounding off decimals to avoid the round-off error. IQRs of ABP intricacy indices and descriptive statistics were evaluated by the quantile function of R
language in type 8 algorithm per R documentation recommendation.

**Results**

Among the 60 enrolled patients, the main indications for liver transplant are acute viral hepatitis and hepatocellular carcinoma (table 1). The acuity of liver disease is relatively mild (MELD-Na: 20.4 [14.4, 31.1]). The MEAF score is 6.21(4.52,7.43, IQR=2.91); the L-GrAFT7 score is -2.54 (-3.12, -1.69, IQR=1.44); the L-GrAFT10 score is -2.45 (-2.97, -1.32, IQR=1.6); the EASE score is -2.19 (-2.84, -1.60, IQR=1.24). There are 5 EAFs (5 mortality, no retransplantation) within POD40. There were 3 cases lacking anhepatic ABP data and 2 cases lacking neohepatic ABP data due to technical issues during the data recording.

**Presurgical ABP intricacy and the acuity condition**

In the presurgical phase, both ABP intricacy indices correlate with MELD score and MELD-Na scores (Fig.2 and supplementary Fig. S2, S3). For the fluctuation movement, the Pearson correlation coefficients (CC) with MELD-Na and MELD score are -0.485 (-0.303, -0.638) and -0.468 (-0.280, -0.625) respectively, whereas for the trend movement, the CC with MELD-Na and MELD scores are -0.505 (-0.327, -0.650) and -0.488 (-0.299, -0.640) respectively. All 4 correlations show p < 0.0001. In addition, the trend movement and fluctuation movement are also correlated with Child-Pugh scores with the Pearson CC -0.442(-0.221, -0.619, P=0.00015) and -0.330 (-0.106, -0.542, P=0.0023) respectively.

In the sensitivity analysis, ABP intricacy indices being derived from various parameters consistently shows higher MELD-Na score correlation than the MELD
score (Fig. S2). Detailed results of the sensitivity analysis and the validation of the quantitative indices are presented in the supplementary.

Fig. 2. The correlation of trend movement (Mov) and fluctuation movement with MELD (Model for End-Stage Liver Disease) and MELD-Na scores in the presurgical phase. The Pearson correlation coefficients, 95% confidence intervals (error bars) and p values in the presurgical, anhepatic, and neohepatic phases are shown. Trend movement correlates best in the presurgical phase but not in the subsequent phases,
whereas the fluctuation movement maintains correlation to the neohepatic phase. As a smaller MELD score indicates a better clinical condition, the ideal correlation coefficient is -1.

**Dynamical changes between surgical phases**

From the presurgical to the anhepatic phase, both ABP intricacy indices decrease significantly and recover partially from the anhepatic to the neohepatic phase (Fig. 3, supplementary Fig. S3). The trend movement indices over the presurgical, anhepatic and neohepatic phases are 88.0 (75.7, 92.3, IQR=16.6), 25.3 (15.7, 40.4, IQR=24.7), and 42.2 (29.0, 64.0, IQR=35.0) respectively. Fluctuation movements over the presurgical, anhepatic and neohepatic phases are 80.7 (63.0, 87.8, IQR=24.5), 20.8 (12.1, 43.6, IQR=31.5), and 48.7 (25.6, 70.1, IQR=44.5) respectively.

However, their correlations with MELD scores behave differently (Fig. 2, supplementary Fig. S3). The correlations of trend movement with the MELD score exhibit larger decrease in the anhepatic phase and no recovery in the neohepatic phase, whereas the correlations of fluctuation movement are relatively maintained (all p values < 0.01) from the presurgical, through anhepatic, to neohepatic phases (Fig. 2).
Fig 3. The trend movements (left panel) and fluctuation movements (right panel) from all cases (60) colored as grayscale lines (darker in higher MELD-Na score) show evolutions among the presurgical, anhepatic, and neohepatic phases. The medians are superimposed in blue and 5 early-allograft-failure (EAF) cases marked by red dotted lines (survival days < 14 days) and yellow dotted lines (survival days > 14 days) are also superimposed. The legend is labeled with the MELD-Na score, where the letter E represents EAF and the following number represents survival days. The graph shows the main findings in this study: 1) higher trend movements in the presurgical phase are associated with lower MELD scores, 2) indices decreased in the anhepatic phase, 3) indices partially recovered in the neohepatic phase, and 4) there is an association of EAF outcome and ABP intricacy at the neohepatic phase.

Association with the surgical outcomes

Five EAF cases present lower trend movements (EAF: 27.2 [9.3, 29.3, IQR=20.0]);
non-EAF: 42.8 [33.2, 64.8, IQR=31.6]) and lower fluctuation movements (EAF: 16.3 [12.6, 27.9, IQR=15.4]; non-EAF: 49.9 [27.6, 70.7, IQR=43.1]) than 55 non-EAF cases.

Regarding the EAF scores, MEAF score is higher in EAF cases (EAF: 8.30 [7.44, 8.57, IQR=1.13]; non-EAF: 5.95 [4.53, 7.02, IQR=2.48]; p=0.07). The 5 EAF cases also present higher L-GrAFT7 score (EAF: 0.0824 [-1.80, 2.19, IQR=3.98]; non-EAF: -2.57 [-3.12, -1.82, IQR=1.30]; p=0.06) and L-GrAFT10 (EAF: 1.16 [-0.576, 3.99, IQR=4.57]; non-EAF: -2.52 [-2.97, -1.64, IQR=1.33]; p=0.05) while the hypothesis test is marginal. The EASE score is consistent with the above (EAF: 1.85 [0.660, 2.01, IQR=2.68]; non-EAF: -2.24 [-2.81, -1.63, IQR=1.17]; p=0.29).

The strongest association of intricacy indices with EAF scores during the neohepatic phase happens when the trend movement and either L-GrAFT score are considered (Fig. 4). Over the neohepatic phase, the trend movement significantly correlates with the L-GrAFT7 score (CC=-0.382 [-0.122, -0.579], P=0.0038), and the L-GrAFT10 score (CC=-0.398 [-0.142, -0.598], P=0.0027) while the correlations between the fluctuation movement and L-GrAFT scores are marginal significant. The correlation between the trend movement and EASE score is marginal while there are no correlations between the intricacy indices and MEAF score.
Fig. 4. Correlations between neohepatic trend and fluctuation movements with early-allograft-failure (EAF) scores, including MEAF (Model for Early Allograft Function) score, the Liver Graft Assessment Following Transplantation risk score in day 7 (L-GrAFT_7) and in day 10 (L-GrAFT_10), and the Early Allograft Failure Simplified Estimation (EASE) score. Error bars indicate 95% confidence intervals. L-GrAFT_7 and L-GrAFT_10 scores correlate better with the trend movement than the other EAF scores and fluctuation movements.

For laboratory data as constituents of EAF scores (Fig. 5), the association with neohepatic trend movements increases day by day. Both total bilirubin and direct bilirubin reach peaks at day 8 (total bilirubin: CC=-0.370 [-0.104, -0.583], P=0.004;
direct bilirubin: CC=-0.386 [-0.113, -0.603], P=0.004) (Fig. 5). The second best neohepatic trend movement correlation is the platelet count, which reaches peak at day 5 with a marginal significance (CC=0.348 [0.587, 0.077], P=0.006). In contrast, the correlations of the neohepatic fluctuation movement and the bilirubin reach peak at day 2 (total bilirubin: CC=-0.338 [-0.097, -0.535], P=0.004; direct bilirubin: CC=-0.326 [-0.094, -0.517], P=0.004) and decrease afterwards. It is worth noting that the correlation between the trend movement and AST peaks at POD3.

**Predict ABP intricacy with MELD score and demographic factors**

To predict the presurgical intricacy indices by the MELD-Na score and demographic data, the linear regression analysis shows MELD-Na is the most significant factor for the trend movements (t=-5.08, p<0.00001, relative importance: 88%), followed by age (t=-2.00, p=0.0498, relative importance: 12%). The BMI and gender are non-significant. Combining all 4 factors in linear regression leads to adjusted R-squared: 0.337 (p<0.00001). For the fluctuation movement, the regression analysis also shows MELD-Na is the most significant factor (t=-4.17, p=0.0001, relative importance: 73%), followed by age (t=-2.61, p=0.011, relative importance: 27%). The BMI and gender are not significant.

**Sensitivity analysis and validation analyses**

The sensitivity analysis shows that the derivation of both indices is robust and insensitive to parameter selection (supplementary Fig. S2, S3). The validation analysis against Null model (Fig. S4) shows decreased association between the meld scores and the presurgical ABP data when the waveform morphology information or the time sequence information was removed. The null model of case labeling shows no association with the MELD scores. The detail results are in the supplementary.
Fig. 5.

The Pearson correlations of the neohepatic ABP intricacy indices with respect to the post-surgical laboratory data as the constituent of the early-allograft-failure scores. Arrows indicate the maximal correlation of total bilirubin (TB) and direct bilirubin (DB) on day 8 and the “negative” platelet count (nPLT) on day 5. The nPLT is to make the platelet count correlation the same direction with all other data for better visualization here as higher platelet means better condition. There are no significant correlations of the alanine aminotransferase (ALT), aspartate aminotransferase (AST), and the international normalized ratio (INR).
Table 1. The demographic data

| Characteristics                  | Number (%) | Median (IQR)       | Mean (SD)     |
|----------------------------------|------------|--------------------|---------------|
| Age, year                        | NA         | 57 (52–62)         | 56.5 (8.4)    |
| Male sex                         | 45 (76.3)  | NA                 | NA            |
| Main indication                   |            |                    |               |
| Viral hepatitis B                 | 36 (61)    | NA                 | NA            |
| Viral hepatitis C                 | 7 (11.9)   | NA                 | NA            |
| Alcoholic cirrhosis              | 9 (15.3)   | NA                 | NA            |
| Other                            | 5 (8.5)    | NA                 | NA            |
| HCC                              | 33 (55.9)  | NA                 | NA            |
| MELD                             | NA         | 18.3 (13.5–28.6)   | 21.0 (11.1)   |
| MELD-Na                          | NA         | 20.4 (14.4–31.1)   | 22.6 (10.7)   |
| GRWR, %                          | NA         | 1.01 (0.88–1.21)   | 1.11 (0.34)   |
| CIT, min                         | NA         | 65 (44–96)         | 76.8 (42.5)   |
| WIT, min                         | NA         | 41 (32–54)         | 44.4 (14.9)   |
| Graft data                       |            |                    |               |
| Type                             |            |                    |               |
| RL without MHV, con(-)           | 27 (45.0)  | NA                 | NA            |
| RL without MHV, con(+)           | 23 (38.3)  | NA                 | NA            |
| RL with MHV                      | 2 (3.3)    | NA                 | NA            |
| LL with MHV                      | 8 (13.3)   | NA                 | NA            |
| Fatty liver, macrovesicular, %   | NA         |                    |               |
| None                             | 25 (41.7)  | NA                 | NA            |
| 1~10                             | 25 (41.7)  | NA                 | NA            |
|   | CIT (h) | GRWR | HCC | LL | MELD | MHV | RL | WIT (h) |
|---|---------|------|-----|----|------|-----|----|---------|
| 11~20 | 8 (13.3) | NA | NA |
| 21~30 | 2 (3.3) | NA | NA |

CIT: cold ischemia time; GRWR: graft-to-recipient weight ratio; HCC: hepatocellular carcinoma; LL: left lobe; MELD: model of end stage liver disease; MHV: middle hepatic vein; RL: right lobe; WIT: warm ischemia time.
Discussion

This is the first study that investigates the pulse-by-pulse temporal evolution of ABP waveform in liver transplant surgery by an unsupervised manifold learning technique. We showed that the ABP intricacy reflects 1) the presurgical condition, 2) the transition between surgical phases, and 3) the early surgical outcome contribution. These support the association between a favorable condition and more ABP waveform evolution intricacy, which is dynamic within a liver transplant surgery. The association between intraoperative ABP waveform and surgical outcome is beyond our expectations.

Presurgical condition

The MELD and MELD-Na scores are used for ranking the urgency of patients awaiting liver transplant surgery. It is also useful for the assessment of various liver diseases, which were formerly served by the Child-Pugh score. Our presurgical results (Fig. 2) show the correlation in the order of the MELD-Na, MELD and Child-Pugh score, which is consistent with the chronological advancement of the above scores developed. It is known that conditions before the transplant surgery do not represent the liver transplant surgical outcome. In our data, the neohepatic trend movement shows no association with the presurgical condition and the presurgical trend movement shows no association with the EAF scores. Our result and evidence suggest that during the presurgical period after the anesthetic induction and before the surgery, the ABP data might be a window to peek into the baseline condition (Fig. 1, Fig. 2). We postulate that patients with lower (better) MELDs possess more homeostatic capability in their cardiovascular system, and thus their ABP waveform
reflects more temporal intricacy.

Transitions in surgical phases

During the anhepatic phase, although we reconstructed the portocaval shunt to release the portal flow, a functioning liver does not exist. The intricacy indices were decreased, especially the trend movement, which recovers partially in the neohepatic phase (Fig. 3). The correlations between the MELD scores and the trend movement were also decreased (Fig. 2). These suggest that the trend movement reflects the dynamics of the pathophysiological condition. In contrast, the correlation between the MELD scores and the fluctuation movement is relatively preserved in the anhepatic and neohepatic phase. This property is not favorable for surgical outcome assessment but worth investigation in the future.

EAD, MEAF, L-GrAFT scores and their constituents

As the presurgical MELD and MELD-Na are not representative of the surgical outcome, laboratory data such as bilirubin have been intensively investigated to assess the graft outcome\(^1\),\(^11\). To extract the underlying information, the EAF scores utilizes not one single spot value, but information from multiple values processed by mathematical formulas involving the area-under-curve summation, maximum, slope and logistic function\(^19\)-\(^21\). Our results show that the neohepatic trend movement is correlated with the L-GrAFT\(_7\), L-GrAFT\(_{10}\), and EASE, but not MEAF score (Fig. 4). It is worth noting that the MEAF score is derived from the laboratory data within POD3 after surgery, including ALT, INR, and bilirubin, while the other later-developed EAF scores weigh more on the laboratory data between POD3 to POD10 and achieve better prognostic performance\(^1\),\(^20\),\(^24\). Moreover, the additional accuracy of L-GrAFT\(_{10}\) score consuming 3 more days laboratory than the L-GrAFT\(_7\) score also justifies the slight better correlation with L-GrAFT\(_{10}\) than that with L-GrAFT\(_7\) score (Fig.4) in this
study. These lines of evidence suggest the connection between intraoperative ABP intricacy and the surgical outcome assessment scores.

Regarding the constituent analyses, the trend movement also correlates best with the POD8 direct bilirubin and indirect bilirubin (Fig. 5), which is similar to the finding reported by Olthoff et al\textsuperscript{1} regarding the POD7 bilirubin > 10mg/dl as one indicator of early graft dysfunction. The authors suggested it represents the graft function rather than the pre-surgical condition. The peak performance with POD8 bilirubin in our study is also in line with the better L-GrAFT\textsubscript{10} accuracy than L-GrAFT\textsubscript{7}, as L-GrAFT\textsubscript{10} contains POD8 bilirubin information. Our result regarding the correlation between POD5 platelet count and the ABP intricacy is in agreement with the previous researches\textsuperscript{25, 26}, where the authors reported that thrombocytopenia (platelet counts < 72500/\textmu L) on POD5 as an independent factor for EAF. Takahashi et al.\textsuperscript{28} suggested that the prognostic effect of thrombocytopenia cannot be simply attributed to presurgical conditions or the postoperative graft function. The platelet may promote liver regeneration. Our result of the correlation between the AST and the trend movement peaks at POD3 (Fig. 5) is in agreement with the prognostic value of POD3 AST, but not POD3 ALT, reported by Robertson et al. in a large scale prospective study\textsuperscript{24, 27}. However, our result is not significant in statistics probably due to the scale of our case number or the minimal ischemia time of the living donor liver transplant.

In summary, the constituent analysis results support the association between the intraoperative ABP intricacy and the graft function recovery, which takes days to reflect in the laboratory data.

**Pathophysiology and clinical implication**

Our results show the ABP intricacy in transplant surgery associated with the presurgical condition, surgical phase transition, outcome scores, and prognostic
laboratory data, the bilirubin and platelet count. Literatures indicated the ABP waveform reflecting information of arterial stiffness, imminent shock, and cardiovascular system profile\textsuperscript{7-10}. Our past study showed the effect of vasoactive medication or noxious stimulation in ABP waveform via manifold learning\textsuperscript{4}. These lines of evidence suggest the regulating mechanism involving multiple organs or systems. To our best knowledge, there is no literature reporting relevant findings. However, a similar notion that more variability or complexity is associated with better vitality has been reported in other biomedical data. The beat-to-beat heart rate variability (HRV) extracted from ECG has been long known to be associated with the autonomic nerve activity, where a larger variability is in general associated with a better outlook\textsuperscript{28, 29}. The blood pressure variability and breathing pattern variability also possess similar notions\textsuperscript{30}. Our null model tests (Fig. S4) shed some light on the blood pressure variability. Replacing waveform with mean blood pressure and perturbating the time sequence information reduce the ABP evolution intricacy to the blood pressure variation. The decreased association with the MELD scores suggests that the waveform morphology information and time sequence information are vital to the evolution intricacy.

On the other hand, it is also known that the renin–angiotensin–aldosterone system is a hormone system regulating the vascular tone, fluid status and electrolyte while the liver produces angiotensinogen. The system possibly contributes the ABP temporal evolution phenomenon. We speculate the regulatory mechanism to maintain homeostasis underpinning these phenomena\textsuperscript{31}. Our result shows that age is also a significant factor of the evolution intricacy while aging is known to diminish the homeostatic regulation. Since the homeostasis physiology involves multiple organs and systems, it is not a trivial task investigating the pathophysiology. The present results also implicate the possible clinical merit in outcome forecast or as an
“real-time liver function index”. A potential parallel to the laboratory examination warrants future clinical study.

Methodological considerations

The temporal evolution intricacy of ABP waveform is an obscure physiological phenomenon. As the pulse-by-pulse change is subtle and complicated, it cannot be easily seen and summarized with naked eyes (Fig.1, Fig. S1). Our results justify the employment of the unsupervised manifold learning method to extract this intricacy information. The ABP waveform analysis has been implicated in hemodynamic problems, ranging from predicting hypotension\(^9\), assessing hemodynamic status\(^7,32-34\), and guiding medical treatment for chronic hypertension\(^8,10\). Most existing ABP waveform analysis techniques, including those embedded in monitoring instruments, require collapsing data within a time frame to obtain a “representative” waveform and/or determine landmark-dependent features. However, as the status of the cardiovascular system is ever-changing, the temporal evolution intricacy information might be collapsed by those techniques. Our previous study\(^4,5\) suggests that any perturbation on the ABP waveform and the subsequent response inevitably produce changes in multiple scales (for example vasoconstriction and cardiac contractility pertain to different scales), which render the basic statistical entities, such as the average or the variance, based on one dimensional scale impractical. Hence, it justifies employing manifold learning to ABP waveform evolution in high-dimensional (multivariate), from which the intricacy indices quantify the overall effect of multiple regulatory mechanisms on ABP waveform morphology. The other advantage is a visualization that helps “grasp the whole picture” to establish the concrete structure in our mind. The 3-D image inspired us to use the notion of movement from the Newtonian mechanics to quantify the trajectory (Fig. 1, Fig. S1).
Limitation and Future Works

There are several limitations in this study. Our EAF case number (5) is not large enough to reach statistical significance with respect to non-EAF group despite the difference in the descriptive statistics. A larger scale study is needed for further factor analysis. Second, we did not collect the postoperative waveform data. As the intra-operative neohepatic ABP information associates with the EAF scores, it is intriguing to suspect that the ABP data during postoperative recovery offer more definite outcome information. Third, our result is obtained from living donor liver transplant. It maybe not representative to cadaver liver transplant as the cold ischemia time is incomparable. Fourth, our methodology involves ABP waveform recording hence it may not be feasible for retrospective research, as most electronic medical records systems do not include waveform data.

In future study, the ABP intricacy in postoperative recovery period deserves to be elucidated. As the surgical phase transition from the anhepatic to neohepatic phase prognosticates the surgical outcome much earlier than the laboratory data, it is mandatory to investigate the possibility of outcome improvement by the timely intraoperative intervention or the early intervention during postoperative recovery. In light of the EAF scores, forthcoming analyses combining ABP evolution and other laboratory data is warranted. We envision the development of an integrated solution for the early outcome prediction and even risk modification via timely assessment in clinical liver transplantation ultimately.

Conclusion

The quantitative intricacy in successive ABP waveform evolution reflects the liver disease severity, dynamically indicates the liver transplant steps, and foretells the short-term surgical outcomes.
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Supplementary materials

The technical perspective of temporal waveform evolution

Through careful visual inspection, we see that the arterial blood pressure (ABP) waveform morphology evolves over time while the human body undergoes events drastically affecting the hemodynamic condition. However, most of the time, the pulse-by-pulse morphologic change is subtle. The pulse waveform manifold learning is the corresponding technique enabling the possible analysis of subtle and long waveforms. What manifold learning contributes to this task is treating each pulse waveform as one data point in the high dimensional space and evaluating the whole waveforms from all points altogether to extract their inner structure. In such a way, the temporal waveform evolution becomes a trajectory formed by successive points on the manifold representing successive pulse waveforms. (Fig. S1) We can analyze the shape of the trajectory to extract the time-evolution. Thanks to the “dimension reduction” property, the trajectory is moving in a space of which the dimensionality is much lower than the original data space, and thereby it is much easier to compute and to analyze.

Meticulous visual inspection of the trajectory presented with manifold learning provides an impression that the intricacy level corresponds to the general condition of the patient undergoing surgery. In particular, the more intricacy in temporal waveform evolution between successive ABP pulses corresponds to the more movement in the trajectory (Fig. 1 and Fig. S1). Furthermore, the short-term fluctuation and the underlying trend seems to behave differently.

Inspired by these impressions, we used the combination of moving median method to extract the trend component movement (slow-varying evolution) and the
fluctuation component (fast-varying evolution). The combination further strengthens the trend representative in various statistical distributions that we currently may not know. Note that the trend component does not mean it move monotonically in one direction while the fluctuation component does not mean it comprises stationary random process as is the common usage in statistics. As both entities measure the amount of the dynamical activity of the trajectory representing the underlying features of those pulse waveforms, we consider them as the quantitative measures of the intricacy notion.

From the machine learning perspective, the DDMap contributes the feature extraction step by directly consuming the raw waveform data and presenting the temporal evolution. The main feature is expressed as the shape of the trajectory (Fig. S1). As the “feature” quantification is efficient, the “parameter training” process is unnecessary in this study. The present approach is unsupervised in nature as the waveforms as data points directly determine the manifold and the trajectory shape without any experts’ label. In other words, there is no other clinical information, or labeling information, or even the time stamp information, to guide the feature learning process.

Due to the approximately isometric property and the algorithm development of the DDMap, the trajectories on the manifold are reliable in both microscopic scale and in macroscopic scale, which became the foundation for our quantitative trajectory analysis based on the notions of Newtonian mechanics.
Fig. S1. The waveform evolution is hard to be observed from the 1-minute tracing (upper) while the 5 minutes data shows the pulse-by-pulse trajectory (middle) in 3-dimensional image via waveform analysis via manifold learning waveform analysis. Local fluctuation and its trend movement. The local fluctuation and the trend movement (lower) further depict the trajectory shape information as quantitative.
intricacy measures, the fluctuation movement and the trend movement.

Pulse Waveform Signal Processing

Driven by the heart beating, pulsation is a universal feature of almost all cardiovascular signals. Denote the ABP waveform signal as $x^A \in \mathbb{R}^N$, where $N$ is the number of sampling points. Since our sampling rate is 300Hz, the signal lasts for $N/300$ seconds. To generate a data point from every pulse, the first step is segmenting $x^A$ into segments. We use the maximum of the first derivation of the ascending part from every ABP waveform as its fiducial point. Denote the $i$-th fiducial point as $n_i$ and suppose there are $L$ pulse cycles in $x^A$. The segmentation provides a collection of consecutive pulses where the $i$-th segment represents one pulse cycle as $\bar{x}^A_i := [x^A(n_i), x^A(n_i + 1), ..., x^A(n_i + q - 1)]^T$, where $q$ is the minimal length of all segments and we use it to truncate each pulse to be of a uniform size. Then, we concatenate four consecutive pulses to enhance their temporal relationship. Finally, we obtain the dataset (or point cloud) $\chi^A = \{(\bar{x}^A_i)^T (\bar{x}^A_{i-1})^T (\bar{x}^A_{i-2})^T (\bar{x}^A_{i-3})^T\}_{i=3}^{L} \subseteq \mathbb{R}^{3q}$. We assume that $\chi^A$ can be represented by a low dimensional manifold, referred to as the wave-shape manifold. The subsequent task is applying the manifold learning algorithm to extract the dynamics.

Dynamic Diffusion Map (DDMap)

We apply manifold learning to study complex information as a shape (manifold) in
high dimensional space. The complex information can be summarized into a 3D image. Dynamic Diffusion map (DDMap) is one of the manifold learning algorithms that is a variant of diffusion map particularly designed for the ultra-long term biomedical signal. The main reason we chose DDMap is its capability to preserve the global structure with rigorous theoretical supports. The first step of DDMap is preparing the point cloud $\chi^A$. Then, take $\chi^A$ to construct an $n \times n$ affinity matrix $W$ so that $W_{ij} = e^{-|x_i-x_j|^2/\epsilon}$, where $i, j = 1, ..., n$ and the bandwidth $\epsilon > 0$ is user defined. In practice, we set $\epsilon$ as the 25% percentile of all pairwise distances.

From the perspective of geometry, $W_{ij}$ contains the information regarding dissimilarities of all two-point pairs; the larger $W_{ij}$ is, the more similar two points are. Next, construct an $n \times n$ degree matrix $D$ so that $D(i, i) = \sum_{j=1}^{n} W(i, j)$, where $i = 1, ..., n$. Using both matrix $W$ and $D$, we obtain the transition matrix $A := D^{-1}W$. It depicts a random walk in the point cloud $\chi^A$ that integrates the geometric structure within the data, and simultaneously suppresses the undesired noise. The eigen-decomposition of $A = U \Lambda V^T$ with eigenvalues $1 = \lambda_1 > \lambda_2 \geq \lambda_3 \geq \cdots \lambda_n$ of $A$ and $\phi_1, \phi_2, ..., \phi_n \in \mathbb{R}^n$ the corresponding eigenvectors. Finally, we get the DDMap as $\Phi_t: x_j \mapsto (\lambda_2^t \phi_2(j), \lambda_3^t \phi_3(j), ..., \lambda_{\hat{d}+1}^t \phi_{\hat{d}+1}(j)) \in \mathbb{R}^{\hat{d}}$, where $j = 1, ..., n$, $t > 0$ is the user-defined diffusion time, and $\hat{d}$ is the user-defined embedding dimension, and note that $j$ represents index of each pulse waveform. We discard $\lambda_1$ and $\phi_1$ as they contain no information. We empirically chose the dimension $\hat{d}$ as 15 or less as the eigenvalues decay fast enough for pulse waveform data so that the eigenvalues of $\hat{d} > 15$ are neglectable. That is, DDMap converts a pulse cycle to a vector that contains 15 parameters. We can then define the diffusion distance (DDist) as the straight line distance between two points $\Phi_t(x_i)$ and $\Phi_t(x_j)$ (technically, the $L^2$ distance) as $D_t(x_i, x_j) := \|\Phi_t(x_i) - \Phi_t(x_j)\|_{L^2}$. We
can use DDist to quantify the similarity between data points, to perform statistical
test between two samples, or perform further signal processing. In this study, the
intricacy measures are based on the DDist.

With DDMap, in practice, we first explore the shape formed by the point cloud by
examining its 3-D scatterplot image by DDMap to grasp the whole picture. We may
choose the diffusion time $t$ as 1 to have the “standard” scale of the image or choose
$0 \leq t < 1$ to watch the detail structure in other coordinates associated with small
eigenvalues that are obscured by those coordinates associated with large eigenvalues.

Next, we explore the dynamics as well as other clinical information by further
interpreting what DDMap presents by DDist.

It is worth noting that there are other manifold learning algorithms. We chose
DDMap currently because it is the algorithm preserves the structure in global scale
and in local scale simultaneously, as well as robust to noise with theoretical
guarantee. We found these merits are indispensable in cardiovascular waveform
analysis empirically.

Trajectory analysis towards intricacy measures

As pulse waves are successive in time, by connecting two consecutive embedded
points, $\Phi_t(x_i)$ and $\Phi_t(x_{i+1})$, we obtain a trajectory $\Psi_1, \Psi_2, \ldots$ in the 15-dim
space, where $\Psi_i = \Phi_t(x_i)$, comprising these pulse points in DDMap (Fig. S1). As the
shape of the trajectory contains the information, we model it as $\Phi_j := T_j +
A_j \theta(\varphi_j) + R_j$, where the trend $T_j$ determines the trajectory’s framework while
the local fluctuation consists of the deterministic oscillatory component
$A_j \theta(\varphi_t(j))$ and $R_j$ represents the stochastic component or any other activity that
cannot be represented by oscillatory activity. The oscillatory component is supposed to be a 1-periodic function \( \theta \) with mean 0 attached with the amplitude \( A_j \) and phase \( \varphi_j \). Based on this model, we applied a moving median followed by a moving mean filter to extract the trend, 
\[
\hat{T}_j := \frac{1}{k} \sum_{m=j-k+1}^{j} \text{Median}(\Psi_m, \Psi_{m-1}, \ldots, \Psi_{m-k+1}),
\]
where both filters are parameterized by the size \( k \). Then we have the fluctuation term \( A_j \theta(\varphi_t(j)) + R_j = \Phi_j - \hat{T}_j \). In this study, we do not further decompose the fluctuation term into \( A_j \theta(\varphi_t(j)) \) and \( R_j \) in the above model, as we focus on observing how the trend and non-trend behave in the real world data. The “pulse-wise” fluctuation movement is calculated as the Euclidean distance between the trajectory and the trend as \( \| \Phi_j - \hat{T}_j \|_2 \). Note that if \( \hat{T}_j = \Phi_m \) for some \( m \), \( \| \Phi_j - \hat{T}_j \|_2 \) is the DDist between \( \Phi_j \) and \( \hat{T}_j \). In this study we use its mean value to represent one intricacy measure within a period.

Another intricacy index, the trend movement, is calculated as the length of the piecewise trajectory path per second as \( (\sum_{i=1}^{L} \| \hat{T}_i - \hat{T}_{i-1} \|_2^2) / T \) for a signal of \( T \) seconds containing \( L \) pulses. We borrow the notion of speed to make this intricacy measure quantify how fast the trend evolving. In summary, both intricacy measures, the trend movement and fluctuation movement, are intuitively derived from the trajectory structure to measure the amount of waveform dynamics.

For the convenience of future clinical application, both indices would be better to be represented in a roughly 0-100 range. Therefore, we pool all ABP data segments (presurgical: 60 cases, anhepatic: 57 cases, neohepatic phase: 58 cases) and employed the formula as follows to remap. The trend movement is calculated as
\[
\frac{\text{row trend movement} - \text{median(pool of row trend movements)}}{\text{IQR(pool of row trend movements)}} \times 25 + 60.
\]
So is the fluctuation
movement. As both median and IQR are calculated with the quantile function, of which the algorithm has several versions in history and produces slightly different values, we standardized it as the type 8 algorithm according to the recommendation of the R documentation.

**Calculation of MELD score and Early Allograft Failure Scores**

Taking care of liver recipients requires intense medical resources and teamwork dedication. From the intraoperative anesthetic management to post-operative follow-up, sometimes the decision making is challenging based on enormous clinical data accumulated over time. Effective data interpretation generates valuable information. While statistical methods require adequate sample size to perform hypothesis tests, introducing new technologies to assess data obtained from each liver recipient may also reveal clinical details.

The MELD and EAF scores, including model for early allograft function (MEAF) score, Early Allograft Failure Simplified Estimation (EASE) score, and the liver graft assessment following transplantation (L-GrAFT7) risk score, were developed based on the laboratory data from a large number of cases to assess the general condition of the liver transplant recipient. As the disease acuity may also compromise numerous physiological mechanisms for homeosis, we propose that the ABP waveforms evolving with time reflect the severity of the patient’s condition, and these scores allow us to investigate the ABP waveform evolution structure with respect to the conditions immediately before the surgery and afterward.

Below we detail these scores. We calculated them according to the formula reported in the corresponding literature and validated by materials provided by the corresponding authors through private communication.

The MEAF score is derived from three laboratory data, ALT, INR, and Bilirubin, within 3 postoperative days. The MEAF score is calculated as:

\[
MEAF = \left( \frac{3.29}{1 + e^{-1.9132(\ln(ALTmax3pod)-6.1723)}} \right) \\
+ \left( \frac{3.29}{1 + e^{-6.8204(\ln(INRmax3pod)-0.6658)}} \right) \\
+ \left( \frac{3.29}{1 + e^{-1.8005(\ln(bilirubin3pod)-1.0607)}} \right)
\]
The L-GrAFT\textsubscript{7} score and L-GrAFT\textsubscript{10} score comprise the laboratory data of AST, INR, total bilirubin, and platelet counts at day 7 and day 10 respectively. We compute L-GrAFT\textsubscript{7} as

\[
6.96470 - 0.57990 \times \sum_{day=1}^{7} \ln \text{AST}_{day} + 0.00844 \times \left( \sum_{day=1}^{7} \ln \text{AST}_{day} \right)^2 + 5.25347 \times \text{Slope} \left( \ln \text{AST}_{day1}, ..., \ln \text{AST}_{day7} \right) + 4.65046 \times \\
\text{Slope} \left( \ln \text{AST}_{day1}, ..., \ln \text{AST}_{day7} \right)^2 + 1.14098 \times \sum_{day=1}^{7} \ln \text{INR}_{day} - 0.03475 \times \sum_{day=1}^{7} \ln \text{TBIL}_{day} + 0.00562 \times \left( \sum_{day=1}^{7} \ln \text{TBIL}_{day} \right)^2 + 4.31135 \times \text{SLOPE} \left( \ln \text{TBIL}_{day1}, ..., \ln \text{TBIL}_{day7} \right) + 5.84724 \times \\
\text{SLOPE} \left( \ln \text{TBIL}_{day1}, ..., \ln \text{TBIL}_{day7} \right)^2 - 0.05115 \times \sum_{day=1}^{7} \ln \text{PLT}_{day},
\]

where \( \ln \) represents the natural logarithmic function, and L-GrAFT\textsubscript{10} is calculated as

\[
9.77 - 0.42946 \times \sum_{day=1}^{10} \log(AST_{day}) + 0.00462 \times \\
\left( \sum_{day=1}^{10} \log(AST_{day}) \right)^2 + 4.60719 \times \text{Slope} \left( \ln \text{AST}_{day1}, ..., \ln \text{AST}_{day7} \right) + 4.4129 \times \text{Slope} \left( \ln \text{AST}_{day1}, ..., \ln \text{AST}_{day7} \right)^2 + 0.88974 \times \\
\text{MAX} \left( \ln \text{INR}_{day1}, ..., \ln \text{INR}_{day10} \right) - 0.04852 \times \sum_{day=1}^{10} \ln \text{TBIL}_{day} + 0.00363 \times \left( \sum_{day=1}^{10} \ln \text{TBIL}_{day} \right)^2 + 5.33627 \times \\
\text{SLOPE} \left( \ln \text{TBIL}_{day1}, ..., \ln \text{TBIL}_{day10} \right) - 0.04621 \times \sum_{day=1}^{10} \ln \text{PLT}_{day} - 5.24897 \times \text{SLOPE} \left( \ln \text{PLT}_{day1}, ..., \ln \text{PLT}_{day10} \right) + 13.08633 \times \\
\text{SLOPE} \left( \ln \text{PLT}_{day1}, ..., \ln \text{PLT}_{day10} \right)^2.
\]

In comparison with the above scores, the EASE score consumes more items, including the laboratory data of AST, platelet, bilirubin within 10 days, the MELD score, the number of transfused packed red bleed cell during surgery, the events of vascular thrombosis within 10 days after the surgery and whether the early volume of the institution is larger than 70 cases per year. It is calculated as

\[
0.000534 \times \\
\text{AUC} \left( \ln \text{AST}_{day1}, \ln \text{AST}_{day2}, \ln \text{AST}_{day3}, \ln \text{AST}_{day7}, \ln \text{AST}_{day10} \right) - 0.093 \times \text{AUC} \left( \ln \text{PLT}_{day1}, \ln \text{PLT}_{day3}, \ln \text{PLT}_{day7}, \ln \text{PLT}_{day10} \right) - 7.766 \times \\
\text{SLOPE} \left( \ln \text{PLT}_{day1}, \ln \text{PLT}_{day3}, \ln \text{PLT}_{day7}, \ln \text{PLT}_{day10} \right) + 0.795 \times
\]

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\[ SLOPE(\ln TBIL_{day1}, \ln TBIL_{day3}, \ln TBIL_{day7}, \ln TBIL_{day10}) + 0.044 \times MELD + 0.065 \times PRBC + 2.567 \times thrombosis - 0.402 \times volume - 0.602, \]

where \( AUC \) represents the area under the curve evaluated by the trapezoid sum, \( thrombosis \) is 1 if arterial or portal thrombosis taken place within 10 days postoperatively and 0 otherwise, and \( volume \) is 1 if the institutional case volume more than or equal to 70 cases per year and 0 otherwise.

**Supplementary Results**

**Sensitivity analysis of MELD score correlations**

In this sensitivity analysis, we test the effect of filter size parameter \( K \), which determines the time scale of both intricacy indices, the fluctuation movement and trend movement. The goal is to confirm if the quantitative indices are sensitive to the chosen parameters/model or not, and how them affect the performance in reflecting the dynamical surgical phases transition from the presurgical phase to anhepatic phase.

For the Pearson correlation between presurgical ABP data and the MELD score (Fig S2), the trend movements achieve statistical significance from all \( K \) (\( K=8 \) to 140) whereas the fluctuation movements become significant from \( K=18 \). The trend movement reaches maximum correlation at \( K=40 \) while the fluctuation movement at \( K=130 \). Both indices show smooth curves in their correlations, indicating the robustness over the \( K \) parameter. For quantifying the smoothness of the curve, all the differences between adjacent correlation coefficients are small for the correlations between MELD and the presurgical fluctuation movement (\( -0.013 [-0.026, -0.006, IQR=0.020] \)), the correlations between MELD-Na and the presurgical fluctuation movement (\( -0.014 [-0.025, -0.007, IQR=0.017] \)), the correlations between
MELD and the presurgical trend movement \((0.0029 \ [-0.0029, 0.009, \text{IQR}=0.012])\), and the correlations between MELD-Na and the presurgical trend movement \((0.0019 \ [-0.0029, 0.009, \text{IQR}=0.012])\).

Fig. S2. The correlation of the trend movement and the fluctuation movement with MELD-Na and MELD (Model for End-Stage Liver Disease) scores in presurgical phase. The Pearson correlation coefficient (CC, solid lines) and their 95% confidence interval (CI, dashed line) shows significance over wide parameter range (arrow line) to the scores. The trend movement (TM) is more stable than the fluctuation movement (FM) in correlation to the MELD scores. The CC and CIs are negative as a smaller MELD score indicates a better clinical condition.

For the changes from the presurgical phase to anhepatic phase (Fig. S3), the sensitivity analysis is consistent with the main finding: the correlations of trend movement with the MELD score exhibit larger decrease in the anhepatic phase and
no recovery in the neohepatic phase, whereas the correlations of fluctuation movement are relatively maintained. The chosen parameter $K=90$ presents the largest drop of the correlation with the MELD and MELD-Na scores, while other $K$ also presents a large drop, which suggests the robustness of both trend movement and fluctuation movement with regard to the choice of $K$. The smooth curves also present the robustness of both indices. We conclude from this sensitivity analysis that the derivation of the ABP intricacy indices would help reveal the temporal evolution structure in ABP data.
Fig. S3. The drop of the MELD correlations (upper panel) from the presurgical (dotted line) to anhepatic phase (solid line) with trend movement (TM) are larger than that with fluctuation movement (FM). For the drop of the correlation of TM (lower panel), parameter \( K=90 \) represents the most dynamical change from the presurgical to anhepatic phase. The arrow indicates the largest decrease at \( K=90 \). The smooth correlation coefficient curves indicate the numeric robustness of both FM and TM indices.

**Null Model Test**

In this null model validation test (Fig. S4), we first replace waveform by mean blood pressure to replace waveform and evaluate the correlation with the MELD scores. For the presurgical phase, compared with the fluctuation movement, the correlation is decreased (MELD-Na: \(-0.450 \rightarrow -0.380\), MELD: \(-0.436 \rightarrow -0.374\)), so is the presurgical trend movement (MELD-Na: \(-0.480 \rightarrow -0.405\), MELD: \(-0.468 \rightarrow -0.395\)). Both maintain statistical significance.

The second null model validation test is the surrogate data test by randomly permuting the time sequence of the ABP pulses. It shows the decreases of correlation for the fluctuation movement (MELD-Na: \(-0.450 \rightarrow -0.389\), MELD: \(-0.436 \rightarrow -0.376\)) and trend movement (MELD-Na: \(-0.480 \rightarrow -0.247\), MELD: \(-0.468 \rightarrow -0.234\)). The trend movement shows a larger drop in the correlation than the fluctuation movement. Both maintain statistical significance.

The third null model validation test is permuting case labeling; that is, random pair MELD scores and ABP waveforms. It shows no correlation in both indices. The loss of association justifies our hypothesis between ABP intricacy and recipient’s acuity condition.
Fig. S4. The null model validation tests of the Pearson’s correlations between MELD scores and the intricacy indices in the presurgical phase with the error bars indicating 95% confidence intervals. By removing waveform information with mean blood pressure, the attenuated associations still show significance, suggesting the contribution of the blood pressure value. By removing the time sequence information between successive pulses, the attenuated associations, suggesting the contribution of variance information. By removing the case MELD score association, the loss of association justifies our hypothesis between ABP intricacy and the acuity condition.