Evolution of minimally invasive techniques and surgical outcomes of ALPPS in Italy: a comprehensive trend analysis over 10 years from a national prospective registry

EVOLUTION OF TECHNIQUES AND SURGICAL OUTCOMES OF ALPPS IN ITALY: A COMPREHENSIVE TREND ANALYSIS OVER 10 YEARS FROM A NATIONAL PROSPECTIVE REGISTRY

Matteo Serenari1,2, Francesca Ratti3, Nicola Guglielmo4, Matteo Zanello5, Federico Mocchegiani6, Jacopo Lenzi7, Michele Colledan8, Vincenzo Mazzaferro9, Umberto Cillo10, Alessandro Ferrero11, Matteo Cescon1,2, Fabrizio Di Benedetto12, Marco Massani13 Marco Vivarelli6, Giuseppe Maria Ettorre4, Luca Aldrighetti3, Elio Jovine5,2 on behalf of the ALPPS Italian Registry

ALPPS Italian Registry Contributors

Raffaele Dalla Valle, Fabio Forchino, Gianluca Grazi, Enrico Gringeri, Salvatore Gruttadauria, Paolo Magistri, Bruno Nardo, Fabrizio Romano, Maurizio Romano, Stefania Scamagni, Andrea Scarinci, Matteo Virdis, Giacomo Zanus (Division of Hepatobiliarypancreatic Unit, IRCCS - Regina Elena National Cancer Institute, Rome, Italy; Department of Medicine and Surgery, Hepatobiliary Surgery Unit, University of Parma, Parma, Italy; School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy; Department of Surgery, UOC Chirurgia Generale “Falcone”, Cosenza, Italy)

1 General Surgery and Transplant Unit, IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Sant’Orsola-Malpighi Hospital, Bologna, Italy

2 Department of Medical and Surgical Sciences, General Surgery and Transplantation Unit, University of Bologna, Italy.

3 Hepatobiliary Surgery Division, San Raffaele Hospital, Milan, Italy.

4 Division of General Surgery and Liver Transplantation, S. Camillo Hospital, Rome, Italy.

5 Department of General Surgery, IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Maggiore Hospital, Bologna, Italy

6 HPB Surgery and Transplantation Unit, Department of Clinical and Experimental Medicine, Polytechnic University of Marche, Ancona, Italy.

7 Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum - University of Bologna, Bologna, Italy

8 Unit of Hepato-biliary Surgery and Liver Transplantation, ASST Papa Giovanni XXIII, Bergamo, Italy.

9 Department of Surgery, Division of HPB, General Surgery and Liver Transplantation, Fondazione IRCCS Istituto Nazionale Tumori di Milano, Milan, Italy.

10 Hepatobiliary and Liver Transplantation Unit, University of Padua, Padua, Italy.

11 Department of General and Oncological Surgery, Mauriziano Hospital "Umberto I", Turin, Italy

12 Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University of Modena and Reggio Emilia, Modena, Italy.

13 Regional Center for HPB Surgery, Regional Hospital of Treviso, Treviso, Italy.

ABSTRACT

INTRODUCTION: Since 2012 data from Italian centers performing **A**ssociating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) have been collected in a prospective national registry. The primary aim of this study was to analyze the trends and the outcomes of ALPPS in Italy over 10-years. The secondary endpoint was to evaluate factors affecting the risk of morbidity/mortality/post hepatectomy liver failure (PHLF) and the allocation to minimally-invasive (MI) approach within the whole series.

METHODS: Data of patients submitted to ALPPS between 2012 and 2021 were identified from the ALPPS Italian Registry and evaluation of time-trends was performed. Uni- and multivariable analysis to fulfill the secondary endpoint was also performed.

RESULTS: During the 10-year period, a total of 268 ALPPS were performed within 17 centers. The number of ALPPS divided by the total number of liver resections performed only slightly declined over the study period (APC=-2.0%, p=0.111). MI approach significantly increased over the years (APC=+49.5, p=0.002). According to multivariable analysis, MI completion of stage 1 was protective against 90-day mortality (OR=0.05, p=0.040) as well as enrollment within high-volume centers for liver surgery (OR=0.32, p=0.009). The use of interstage hepatobiliary scintigraphy was the only predictor of PHLF (OR=0.40, p=0.026).

CONCLUSION: This national multicenter study showed that use of ALPPS only slightly declined over the years with an increased use of MI techniques, leading to lower 90-day mortality. PHLF still remains an open issue in ALPPS and the use of interstage HBS is recommended as well as performing ALPPS in experienced centers.

INTRODUCTION

The first description in 2007 at the University of Regensburg passing through the first large series published in 2011[1] and the subsequent foundation of the International Registry[2], up to the publication of the results of the first Randomized Controlled Trial (Ligro trial) [3] were the overall milestones in the fascinating and troubled history of ALPPS. Despite the pervasive enthusiasm for a new technique with the recognized potential to increase the resectability rate of liver cancer and to expand the pool of patients eligible for curative treatment, on the other hand, persistent concerns were raised about the safety profile of this procedure.

The reaction of the HPB community was to provide recommendations on the use of this approach, aiming to maintain acceptable morbidity and mortality rates: hence, the first International consensus was held in Hamburg in 2015 and the conclusions of this meeting were subsequently published in 2016 [4], thus becoming available on a large scale. In Italy the same desire to track and study the use, outcomes and evolutions of this technique has led to the implementation of a dedicated Registy [5], which has traced the national ALPPS trends over the years and constituted the basis for specific studies [6]. All hepatobiliary centers in Italy were indeed contacted in January 2012 and offered the opportunity to participate in a national ALPPS Registry [5].

Across these 10 years, ALPPS has resulted in the description of alternative non-surgical techniques with the rationale of being less invasive such as combining PVE (portal vein embolization) with partial parenchymal transection (PPT). On the other hand, the use of minimally invasive surgical approaches, laparoscopic and robotic, has also penetrated the ALPPS experience [6].

The primary aim of this study was to analyze the trends and the outcomes of ALPPS over 10-year on a national basis. A stratification of the study period according to the publication of the recommendations (2016) after the Hamburg consensus was also made to evaluate the overall impact of the International Consensus. The secondary endpoint was to evaluate factors, within a uni- and

multivariable analysis, affecting the risk of morbidity/mortality/post hepatectomy liver failure (PHLF) and the allocation to minimally-invasive approach within the whole series.

MATERIAL AND METHODS

Study design

Data of patients enrolled in the ALPPS Italian Registry from its establishment (September 2012) to December 2021 were identified and constituted the study population. Patients with less than 3 months of follow up were excluded. Detailed characteristics of the ALPPS Italian Registry are described elsewhere: briefly, it is a prospective intention-to-treat Registry open to inclusion of cases from any Italian center performing ALPPS, without any restriction criteria based on the numerosity of ALPPS performed. The ALPPS Italian registry was approved by the individual ethical committee of each center. Data entered into an anonymized database were monitored by the study coordinator in Maggiore Hospital to check for data completeness and rule out an abnormal rate of missing variables.

To fulfill the *primary endpoint*, time-trend evaluation was conducted analyzing per year:

a) the number of centers performing ALPPS
b) the number of ALPPS performed/divided by the total number of hepatic resections (HR) performed in each center
c) the use of minimally-invasive techniques
d) the incidence of major morbidity, PHLF and 90-day mortality

A time threshold based on the year of publication of the recommendations from Oldhafer et al. [4] was also used to divide the study population into 2 eras (2012-2016; 2017-2021) and to compare surgical techniques and outcomes between them.

To achieve the *secondary endpoint,* all perioperative factors potentially affecting the risk of morbidity/mortality/PHLF and all the preoperative factors potentially affecting the enrollment to minimally-invasive techniques were screened and entered the uni- and multivariable analysis.

Variables

Complications were classified according to the Clavien classification[7] of surgical complications: those graded ≥IIIA were considered a "major" complication. Posthepatectomy liver failure (PHLF) was classified according to the ISGLS definition [8] but only clinically significant PHLF (grade B/C) were considered. Mortality was defined as any death occurring during the interval of both stages or within 90 days after stage 2.

Liver remnant volumes were assessed using cross-sectional imaging by computed tomography (CT) and standardized future liver remnant (sFLR) was assessed in each patient using the Vauthey formula: −794.41 + 1267.28 × body surface area (m2).[9] FLR/BW was calculated as the ratio (%) between FLR volume and patient's body weight (BW), assuming a mean physical liver density of 1.00 g/mL.[10] Interstage hepatobiliary scintigraphy (HBS) was performed according to single institution protocols, together with liver volumetry, to assess liver function before proceeding to stage 2.[11]

High-experienced MILS center were defined as centers performing on average over the 10-year period at least 30% of their cases by MI approach (laparoscopic and/or robotic).[12] High-volume centers were defined as those performing on average over the 10-year period >100 HRs per year.[13] Total number of HR per year was also provided by each center in order to calculate the ratio ALPPS/HR.

Surgical technique

Participation to the ALPPS Italian Registry did not superimpose a specific surgical technique, that was defined according to single institutions preference and protocols. The nomenclature defined in

the first report from the International ALPPS registry was used to describe ALPPS resection types[14]. Partial ALPPS was performed in the same setting as complete ALPPS with PPT as the only difference (i.e. transection down to the level of hepatic veins without compromising hepatic inflow or outflow [4]).

Statistical analysis

Differences in baseline characteristics of patients across the 2 eras were assessed using the Mann–Whitney test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, as appropriate. A time-trend analysis was performed using the annual percent change (APC) as the summary measure for the rate of change over the period 2012–2020. In our analysis, the APC was estimated by fitting a log-linear regression model, assuming the heteroscedasticity and uncorrelation of the random errors based on the Poisson distribution. Time-trend analysis was conducted with Joinpoint Regression Program V.4.8.0.1 (April 2020; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute).

Univariable logistic regression analysis was used instead for the independent effects of considered variables on inclusion to MILS, major morbidity, 90-day mortality and PHLF. All variables associated at univariable analysis with a p-value <0.20 were included in the multivariable analysis. The variables were entered into a backwards stepwise logistic regression for the final model. Predictors were discarded at a p-value >0.20. To allow for the convergence to finite estimates in conditions of separation because of the rarity of some of the potential outcomes, a penalized Firth logistic regression was used. All data were analyzed using Stata version 15 (StataCorp. 2017. *Stata Statistical Software: Release 15.* College Station, TX: StataCorp LP). All tests were two-sided and the significance level was set at 5%.

RESULTS

During the 10-year period, a total of 268 ALPPS were performed within 17 centers active in the ALPPS Italian Registry, providing their data on an intention-to-treat basis. Overall, 247 out of 268 (92.2%) were successfully completed. Within centers participating to the Registry, 10 out of 17 (58.8%) were high-experienced MILS centers whereas 7 out of 17 (41.2%) were high-volume centers for liver surgery. The baseline characteristics of the 268 study patients, overall and before/after 2016, are shown in Table 1.

Trends

The number of centers performing ALPPS did not significantly change over the years (APC=+0.6%, 95% CI -0.47% to +6.2%, p=0.797) (**Figure 1a**). The total number of ALPPS procedures increased from 22 in 2012 to 28 in 2020 (APC=+3%, 95% CI -1.3% to +7.5%, p=0.146) (**Figure 1b**). However, dividing the number of ALPPS by the total number of liver resections performed, ALPPS/HR slightly declined over the study period (APC=-2.0%, 95% CI -4.6% to +0.6%, p=0.111) (**Figure 1c**).

Trends in the proportion of each indication were then evaluated to assess general shifts in utilization of ALPPS for most common liver tumors. PHCC (APC=-6.1%, 95% CI -22.7% to +13.9%, p=0.462) decreased over time. A less pronounced decrease was observed for CLRM (APC=-1.8%, 95% CI -6.3% to +3%, p=0.398) whereas IHCC (APC=+3.7%, 95% CI -5.6% to +13.8%, p=0.392) and HCC (APC=+5.8%, 95% -5.8% to +18.7%, p=0.289) increased over the years. (**Figure 2**)

Progressively, MI approach of stage 1 was more frequently adopted and significantly increased over the years (APC=+49.5, 95% CI +22.2% to +83%, p=0.002) (**Figure 3a**). Forty-seven out of 268 (17.5%) cases were approached by MI technique (41 laparoscopic and 6 robotic). Of them, 2 (4.3%) were converted to open due to bleeding (n=1) and adhesions (n=1). Overall, 29 patients received MI approach for the second stage (10.8% of the whole ALPPS series). Twenty-eight out of the 45 patients (62.2%) who completed the stage-1 by MI technique, were approached by MI technique

also at the second stage (25 laparoscopic, 3 robotic) (**Figure 3b**). Among them, 8 out 28 (28.6%) were converted: reasons for conversion were adhesions (n=4), bleeding (n=3) and oncological concerns (n=1). Only one patient was received laparoscopic resection at the second stage after an initial open first stage.

Ninety-day mortality slightly declined over the study period (APC=-3.1%, 95% CI -12.4% to +7%, p=0.474) (**Figure 4a**). Post-hepatectomy liver failure (following stage 2) decreased from 45.5% in 2012 to 26.1% in 2020 (APC=-7.2%, 95% CI -12.5% to +0.6%. p=0.067) (**Figure 4b**) as well as major morbidity from 52.4% in 2012 to 28.5% in 2020 (APC=-6.6%, 95% CI -12.9% to 0.2%, p=0.056) (**Figure 4c**).

Comparison of the 2 eras (2012-2016 vs. 2017-2021)

When comparing the 2 eras in terms of preoperative characteristics, only ASA score was significantly different with less comorbid patients (ASA 1-2) operated in the second era (60.6% vs. 72.9%, p=0.033) (**Table 1**). In stage 1 (**Table 2**), MI approach (5.2% vs. 30.1%) together with partial parenchymal transection of the liver (23% vs. 45.9%) and PVE (7.6% vs. 29.5%) were significantly more frequently performed in the second era. Also, discharge after stage 1 was significantly more implemented after 2016 (10.4% vs. 43.6%, p<0.001) as well as the use of HBS functional assessment (3.7% vs. 31.6%, p<0.001). Following Stage 1, after 2016 Stage 2 was performed in median 4 days later (11 vs. 15 days, p<0.001) (**Table 3**). MI approach of stage 2 was also more frequently performed in the second era (0.8% vs. 23.3%, p<0.001). Among analyzed outcomes, major morbidity was significantly reduced in the second compared to the first era (36.2% vs. 24.2%, p=0.039). Hospital stays was significantly shorter after 2016 (23 vs. 20 days, p=0.012).

Multivariable analysis

Multiple logistic analysis demonstrated which variables – among those considered - were independent risk factors for major morbidity, 90-day mortality and PHLF. **(Table 4)** In particular,

biliary tumors were predictors of both higher complications (OR=3.28, 95% CI 1.82-5.88, p<0.001) and mortality (OR=4.67, 95% CI 1.88-11.58, p<0.001). MI completion of stage 1 was protective against 90-day mortality (OR=0.05, 95% CI 0.003-0.95, p=0.040) as well as enrollment within high-volume centers for liver surgery (OR=0.32, 95% CI 0.14-0.74, p=0.009). The use of interstage HBS was the only predictor of PHLF (OR=0.40, 95% CI 0.002-0.68, p=0.026). Inclusion to MILS was significantly predicted by 2017-2021 era (OR=8.22, 95% CI 3.46-19.55, p<0.001) and by enrollment from high-experienced MILS centers (OR=5.74, 95% CI 1.29-25.57, p=0.022).

DISCUSSION

The current study showed that use of ALPPS in Italy slightly decreased over the last 10 years since its introduction. Conversely, a significant and increasing trend was observed with regard to the MI approach of ALPPS, which in turn was able to lower 90-day mortality. After the 2016 consensus, there was also a significantly higher implementation of interstage functional assessment which was found to be the only prognostic factor for PHLF.

After the first report of in-situ splitting in 2012[1], ALPPS became one of the most promising surgical techniques in the field of liver surgery. However, despite the early enthusiasm around ALPPS which led also to the creation of an International Registry[2], the first published series showed a very high rate of mortality and morbidity.[14] ALPPS registries were able to demonstrate that complications were mostly related to unfavourable baseline patient characteristics. In particular, biliary tumors, older age and decrease of liver function in the interstage were recognized as the most relevant predictors of ALPPS mortality.[5,15] For this reason, some modifications of the original technique, such as the mini-ALPPS (PVE+PPT) [16] or the use of interstage HBS[17], have been proposed aiming to improve these outcomes. Some of them were discussed during the International Consensus held in 2015 and translated into recommendations published finally in 2016.[4]

The ALPPS Italian Registry was born together with the initial implementation of the original technique, in an era still far from the recognition of the transversal importance of registries on a national and international scale. The creation of a national Registry specifically dedicated to ALPPS constituted a significant event as it represented the historical basis to follow the trends and evolutions of this technique in Italy, a country where hepatic surgery is performed by centers with heterogeneous features in terms of volume of activity, penetration of the minimally invasive approach and characteristics of patients and disease treated.[18] It was created maintaining the criteria of inclusiveness (using broad inclusion criteria and few exclusion criteria) and representativeness (to provide a reliable representation of the national picture), which currently constitute - 10 years after its foundation - the prerequisite for being able to pursue the primary and secondary objectives of this study.

Although recent studies showed a non-inferiority of ALPPS compared to the classical two-stage approach[3], the role of ALPPS has seemed to be cast aside in the recent years. However, that was not fully confirmed in our study where the number of ALPPS (divided by the number of HR) only slightly decreased over the 10 year period, showing that the room dedicated to ALPPS in the daily practice of surgeons, at least in Italy, still exists. What significantly changed, as showed in our study, were the technical modifications of the original technique. In particular, MI approach was increasingly proposed over the years. Laparoscopic and, more recently, robotic techniques have become more and more widespread in liver surgery and now, they have been gaining an ever increasing interest also in this field.[19,20] The use of less-invasive techniques to perform the first stage of ALPPS has been showed in other studies to decrease the overall impact of surgery irrespectively from the approach chosen for stage 2.[6] Its increasing popularity might be explained also by the higher feasibility of the procedure at least compared to a second stage major hepatectomy and our multivariable analysis demonstrated that centers with higher experience in MILS resulted more prone to favor this approach starting from 2017. MI second stage instead, given its higher technical complexity related with reiterative surgery together with baseline

difficulties described in right-sided hepatectomies, has been reported so far only within monocenter case series.[21,22] However, in our study, MI approach of stage 2 was attempted in almost two-thirds of MI first stages, confirming the growing interest in completing laparoscopically or robotically the procedure. Although the risk of conversion in ALPPS still remains significant and higher compared with average conversion rates in MILS, conversion did not significantly affect the risk of morbidity and/or mortality, justifying that approach.[23]

As stated above, MI approach of stage 1 of ALPPS has been showed to decrease the overall impact of surgery. Similarly, in our study, MI completion of stage 1 was found to be significantly associated with decreased 90-day mortality, together with other well-known risk factors such as biliary tumor and older age. Besides that, high-volume centers were found to be protective against 90-day mortality, suggesting that ALPPS should be performed not only by expert surgeons but also in the context of hospitals which can provide the best care for these complex patients especially when these patients develop any kind of complications.[24]

Last but not least, the only predictor of PHLF was the use of interstage HBS. Some preliminary reports were published in this regard [25,26]and all of them have in common that the discrepancy observed between function and volume is particularly over-represented in such a kind of surgery compared to one stage resections, thus making HBS a useful tool in this setting. HBS led to a downward trend of PHLF over the years showing the steepest learning curve among all the outcomes analyzed in our study. Multivariable analysis confirmed the fundamental role of HBS in ALPPS even though clear cutoffs for a safe second stage have not yet been established in this field.[27]

Due to the specific focus of the Registry on ALPPS since its foundation, the main limitation of the present report is the impossibility to evaluate the time trends and outcomes in relationship with the use of conventional techniques for liver hypertrophy and with new emerging technique. This limit

may constitute the basis for the implementation of more comprehensive registries on liver hypertrophy techniques.

In conclusion, this study showed that use of ALPPS remained stable over the years with the introduction of several modifications of the original technique. Among them, an increased use of less-invasive techniques was evident leading also to improved 90-day mortality. PHLF still remains an open issue in ALPPS and the use of interstage HBS is always highly recommended as well as performing ALPPS in experienced centers.

REFERENCES

1 Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, *et al.* Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* [Internet]. 2012 Mar [cited 2016 Jun 19]; **255**: 405–414. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22330038

2 De Santibañes E, Clavien PA. Playing play-doh to prevent postoperative liver failure: The 'aLPPS' approach [Internet]. Ann. Surg. 2012 [cited 2016 Jul 18]. p. 415–417. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22330039

3 Sandström P, Røsok BI, Sparrelid E, Larsen PN, Larsson AL, Lindell G, *et al.* ALPPS Improves Resectability Compared with Conventional Two-stage Hepatectomy in Patients with Advanced Colorectal Liver Metastasis: Results from a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial). *Ann Surg* [Internet]. 2018 May [cited 2018 Apr 26]; **267**: 833–840. Available from: http://insights.ovid.com/crossref?an=00000658-900000000-95903

4 Oldhafer KJ, Stavrou GA, Van Gulik TM, De Santibanes E, Malago M, Schadde E, *et al.*

ALPPS - Where do we stand, where do we go? Eight recommendations from the first international expert meeting. *Ann Surg* [Internet]. 2016; **263**: 839–841. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000658-201605000-00003

5 Serenari M, Zanello M, Schadde E, Toschi E, Ratti F, Gringeri E, *et al.* Importance of primary indication and liver function between stages: Results of a multicenter Italian audit of ALPPS 2012-2014. *Hpb*. 2016; **18**: 419–427.

6 Serenari M, Ratti F, Zanello M, Guglielmo N, Mocchegiani F, Di Benedetto F, *et al.* Minimally Invasive Stage 1 to Protect against the Risk of Liver Failure: Results from the Hepatocellular Carcinoma Series of the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy Italian Registry. *J Laparoendosc Adv Surg Tech*. 2020; **30**: 1082–1089.

7 Clavien PA, Barkun J, De Oliveira ML, Vauthey JN, Dindo D, Schulick RD, *et al.* The clavien-dindo classification of surgical complications: Five-year experience. Ann. Surg. 2009. p. 187–196.

8 Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, *et al.* Posthepatectomy liver failure: A definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011; **149**: 713–724.

9 Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, *et al.* Standardized measurement of the future liver remnant prior to extended liver resection: Methodology and clinical associations. *Surgery*. 2000; **127**: 512–519.

10 Lemke AJ, Hosten N, Neumann K, Müller B, Neuhaus P, Felix R, *et al.* CT-Volumetrie der Leber vor Transplantation. *RoFo Fortschritte auf dem Gebiete der Rontgenstrahlen und der Neuen Bildgeb Verfahren*. 1997; **166**: 18–23.

11 de Graaf W, van Lienden KP, Dinant S, Roelofs JJTH, Busch ORC, Gouma DJ, *et al.* Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. *J Gastrointest Surg*. 2010; **14**: 369–378.

12 Zwart MJW, Görgec B, Arabiyat A, Nota CLM, van der Poel MJ, Fichtinger RS, *et al.* Pan-European survey on the implementation of robotic and laparoscopic minimally invasive liver surgery. *HPB*. 2022; **24**.

13 Torzilli G, Viganò L, Giuliante F, Pinna AD. Liver surgery in Italy. Criteria to identify the hospital units and the tertiary referral centers entitled to perform it. *Updates Surg*. 2016; **68**: 135–142.

14 Schadde E, Ardiles V, Robles-Campos R, Malago M, Machado M, Hernandez-Alejandro R, *et al.* Early survival and safety of ALPPS first report of the international ALPPS registry. *Ann Surg* [Internet]. 2014; **260**: 829–838. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25379854

15 Schadde E, Raptis DA, Schnitzbauer AA, Ardiles V, Tschuor C, Lesurtel M, *et al.* Prediction of mortality after ALPPS Stage-1. *Ann Surg* [Internet]. 2015 Nov [cited 2016 Jun 19]; **262**: 780–786. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26583666

16 de Santibañes E, Alvarez FA, Ardiles V, Pekolj J, de Santibañes M. Inverting the ALPPS paradigm by minimizing first stage impact: the Mini-ALPPS technique. *Langenbeck's Arch Surg* [Internet]. Langenbeck's Archives of Surgery; 2016; **401**: 557–563. Available from: http://dx.doi.org/10.1007/s00423-016-1424-1

17 Serenari M, Collaud C, Alvarez FA, De Santibañes M, Giunta D, Pekolj J, *et al.* Interstage Assessment of Remnant Liver Function in ALPPS Using Hepatobiliary Scintigraphy: Prediction of Posthepatectomy Liver Failure and Introduction of the HIBA Index. *Ann Surg*. 2018; **267**: 1141–1147.

18 Aldrighetti L, Ratti F, Cillo U, Ferrero A, Ettorre GM, Guglielmi A, *et al.* Diffusion, outcomes and implementation of minimally invasive liver surgery: a snapshot from the I Go MILS (Italian Group of Minimally Invasive Liver Surgery) Registry. *Updates Surg*. 2017; **69**: 271–283.

19 Melandro F, Giovanardi F, Hassan R, Larghi Laureiro Z, Ferri F, Rossi M, *et al.* Minimally Invasive Approach in the Setting of ALPPS Procedure: a Systematic Review of the Literature. J. Gastrointest. Surg. 2019. p. 1917–1924.

20 Michal K, Sau M, Tamara GMH, Long JR. A better route to ALPPS: minimally invasive vs open ALPPS. Surg. Endosc. 2020. p. 2379–2389.

21 MacHado MAC, Makdissi FF, Surjan RC. Totally laparoscopic ALPPS is feasible and may be worthwhile. Ann. Surg. 2012.

22 Di Benedetto F, Assirati G, Magistri P. Full robotic ALPPS for HCC with intrahepatic portal vein thrombosis. *Int J Med Robot Comput Assist Surg* [Internet]. John Wiley and Sons Ltd; 2020 Apr 1 [cited 2020 Jun 26]; **16**. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.unibo.it/32011081/

23 Halls MC, Cipriani F, Berardi G, Barkhatov L, Lainas P, Alzoubi M, *et al.* Conversion for Unfavorable Intraoperative Events Results in Significantly Worst Outcomes During Laparoscopic Liver Resection: Lessons Learned From a Multicenter Review of 2861 Cases. *Ann Surg*. 2017;

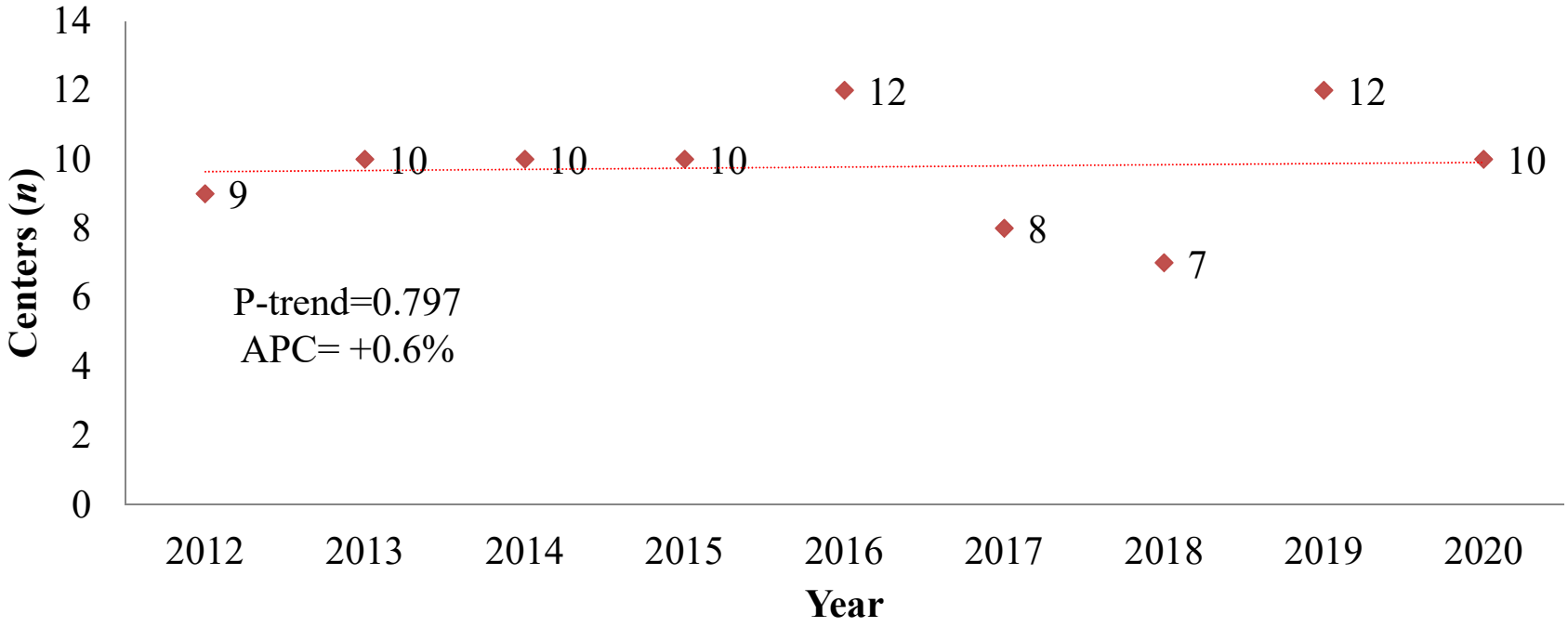
24 Ardito F, Famularo S, Aldrighetti L, Grazi GL, DallaValle R, Maestri M, *et al.* The Impact of Hospital Volume on Failure to Rescue after Liver Resection for Hepatocellular Carcinoma: Analysis from the HE.RC.O.LE.S. Italian Registry. *Ann Surg*. 2020; **272**: 840–846.

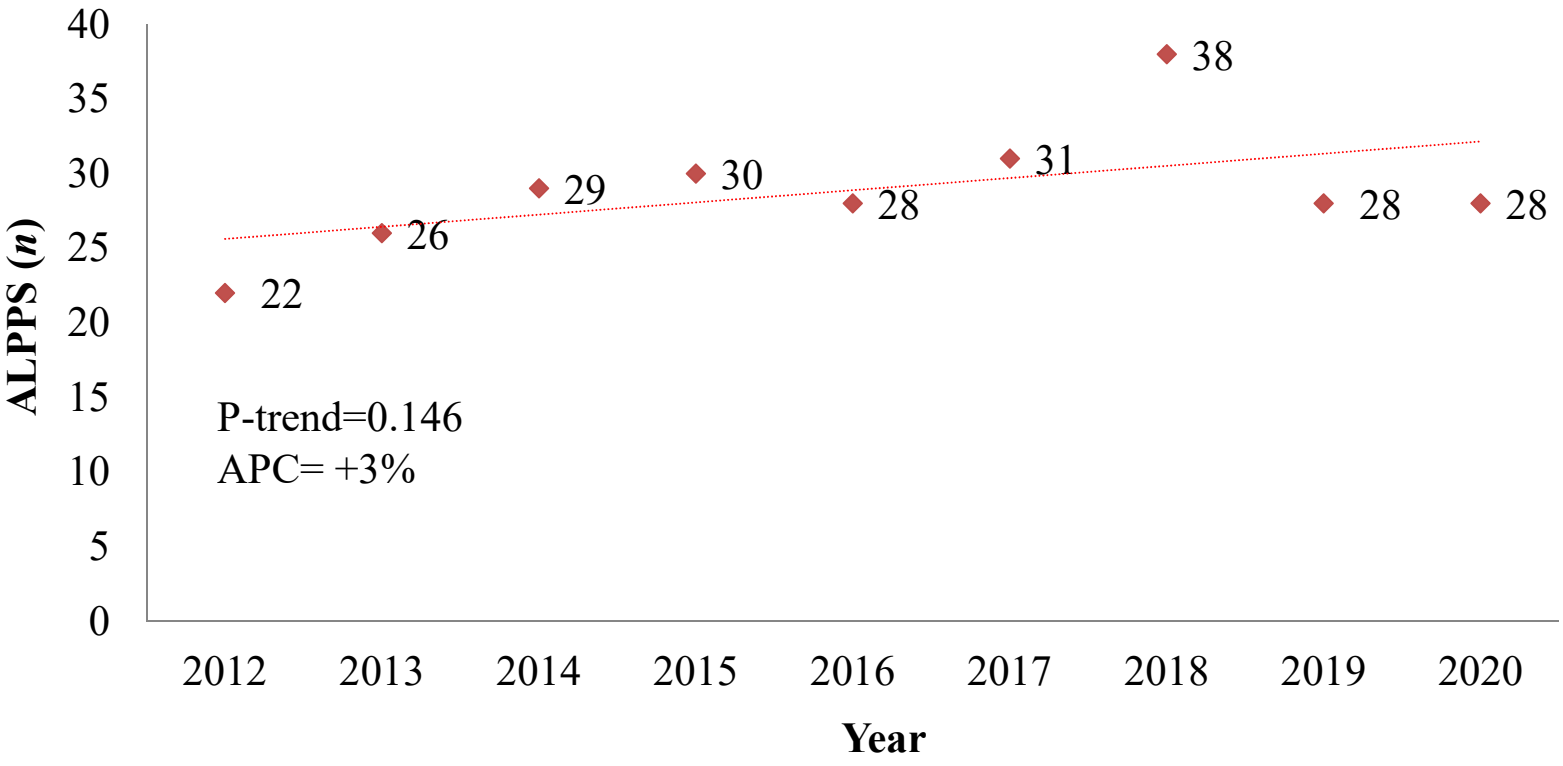
25 Serenari M, Pettinato C, Bonatti C, Zanoni L, Odaldi F, Cucchetti A, *et al.* Hepatobiliary

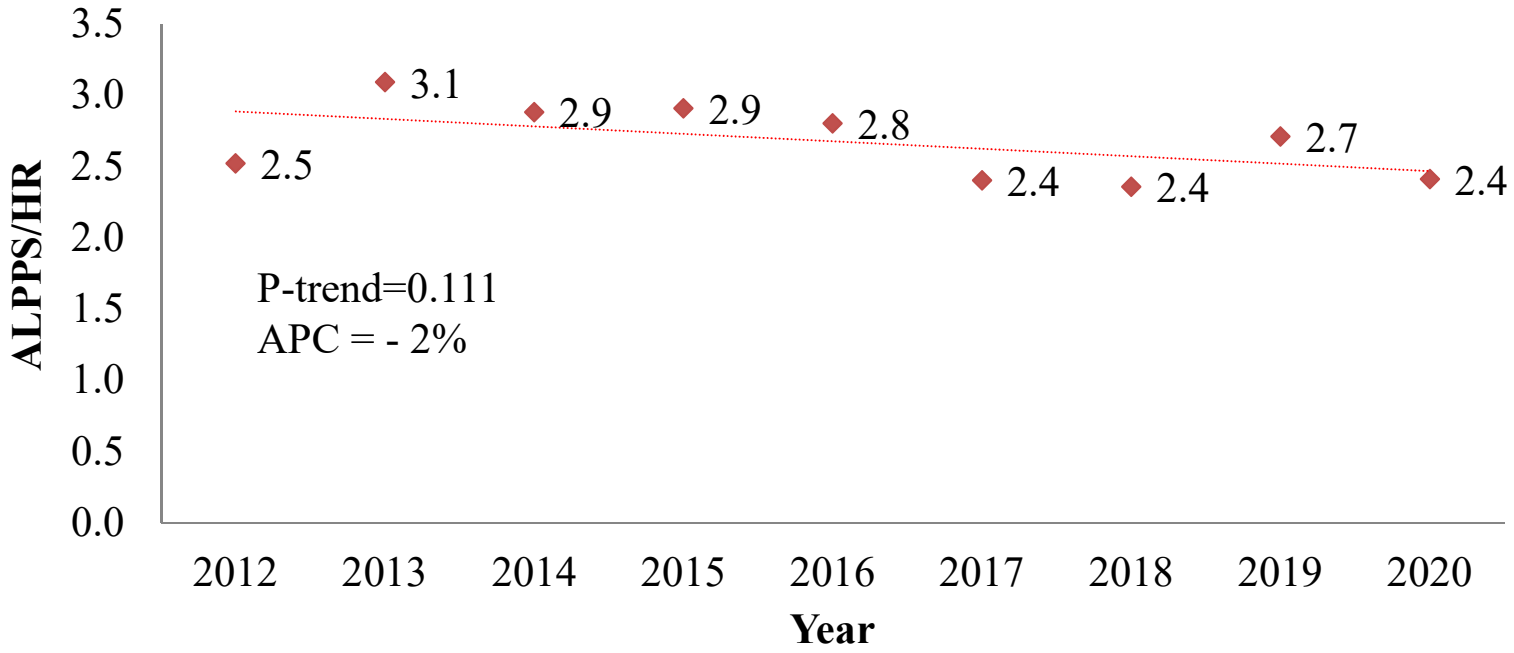
Scintigraphy in the Preoperative Evaluation of Potential Living Liver Donors. *Transplant Proc* [Internet]. Elsevier; 2019 Jun 30 [cited 2018 Aug 27]; **51**: 167–170. Available from: https://www.sciencedirect.com/science/article/pii/S0041134518308753

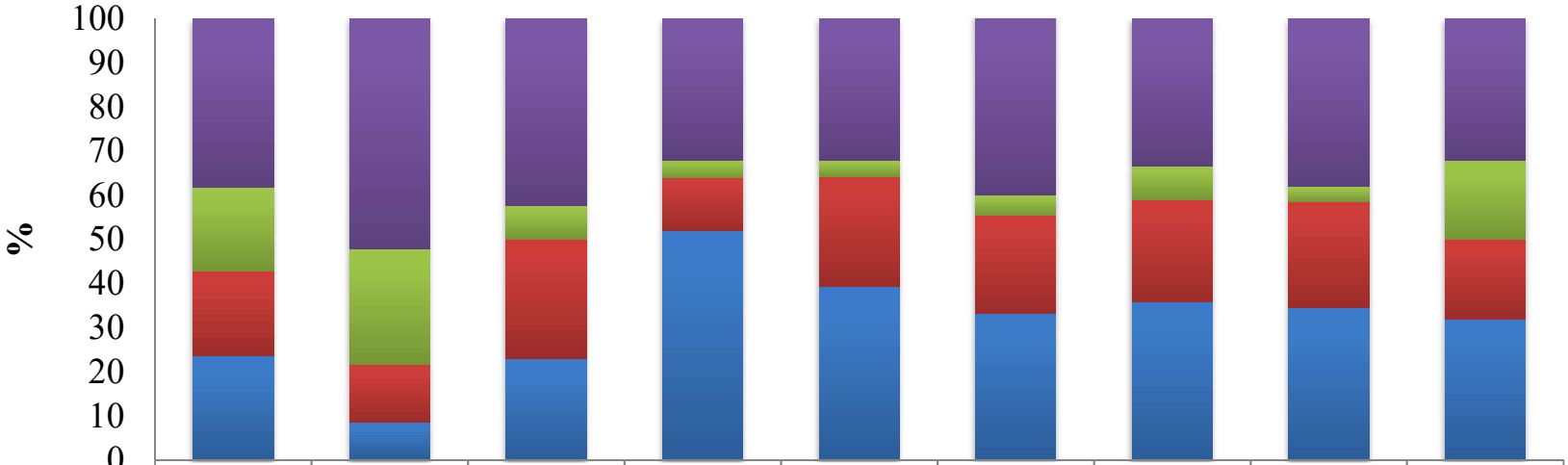
26 Sparrelid E, Jonas E, Tzortzakakis A, Dahlén U, Murquist G, Brismar T, *et al.* Dynamic Evaluation of Liver Volume and Function in Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy. *J Gastrointest Surg*. 2017; **21**: 967–974.

27 Serenari M, Bonatti C, Zanoni L, Peta G, Tabacchi E, Cucchetti A, *et al.* The role of hepatobiliary scintigraphy combined with spect/ct in predicting severity of liver failure before major hepatectomy: a single-center pilot study. *Updates Surg*. 2021; **73**: 197–208.

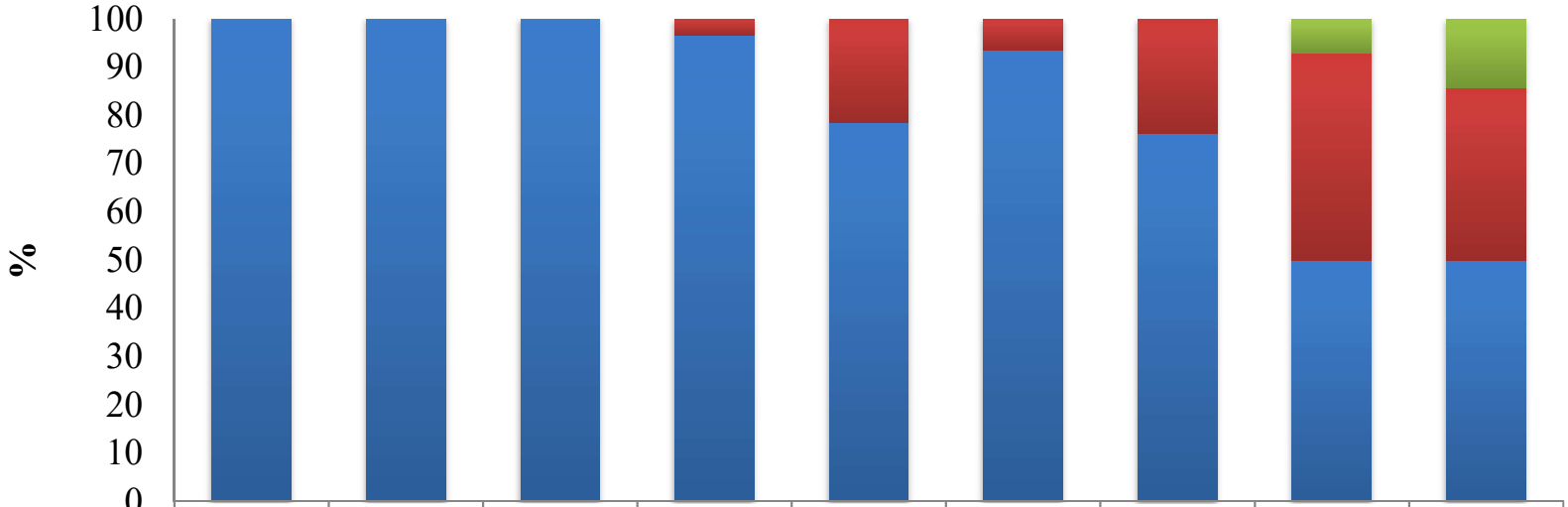

14
12
10
8
6
4
2
0
Centers (n)
9
10
10
10
12
8
7
12
10
P-trend=0.797
APC= +0.6%
2012
2013
2014
2015
2016
2017
2018
2019
2020
Year


40
35
30
25
20
15
10
5
0
ALPPS (n)
38
31
29
30
28
26
28
28
22
P-trend=0.146
APC= +3%
2012
2013
2014
2015
2016
2017
2018
2019
2020
Year

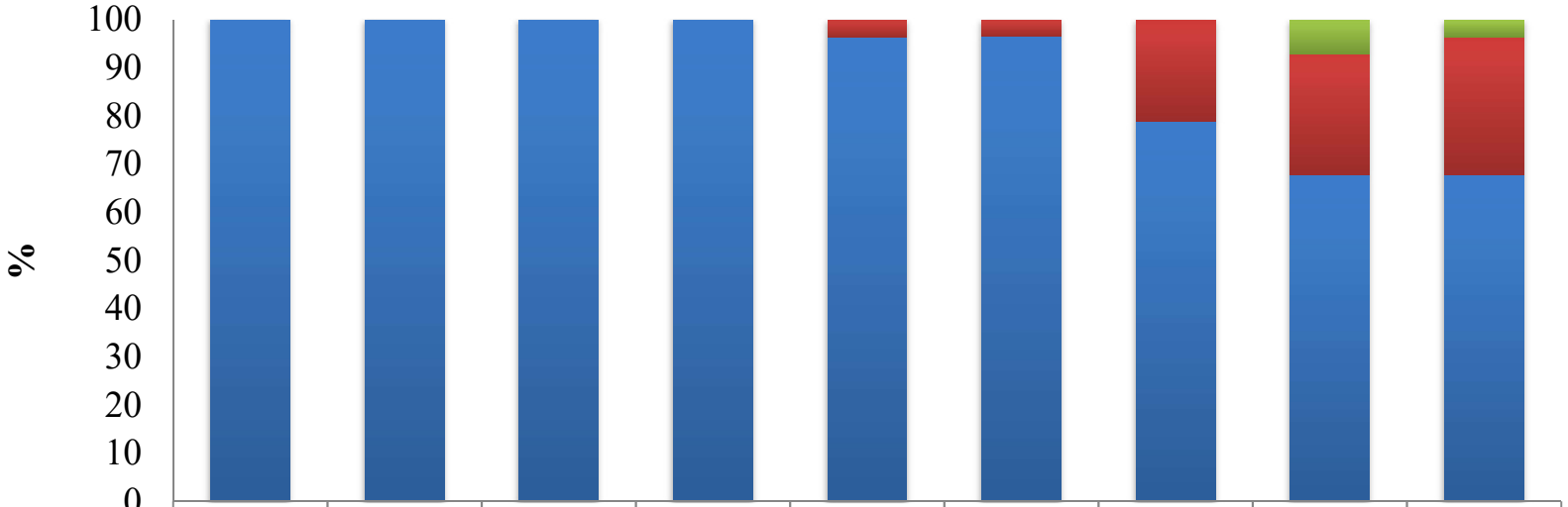

3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ALPPS/HR
2.5
3.1
2.9
2.9
2.8
2.4
2.4
2.7
2.4
P-trend=0.111
APC = - 2%
2012
2013
2014
2015
2016
2017
2018
2019
2020
Year



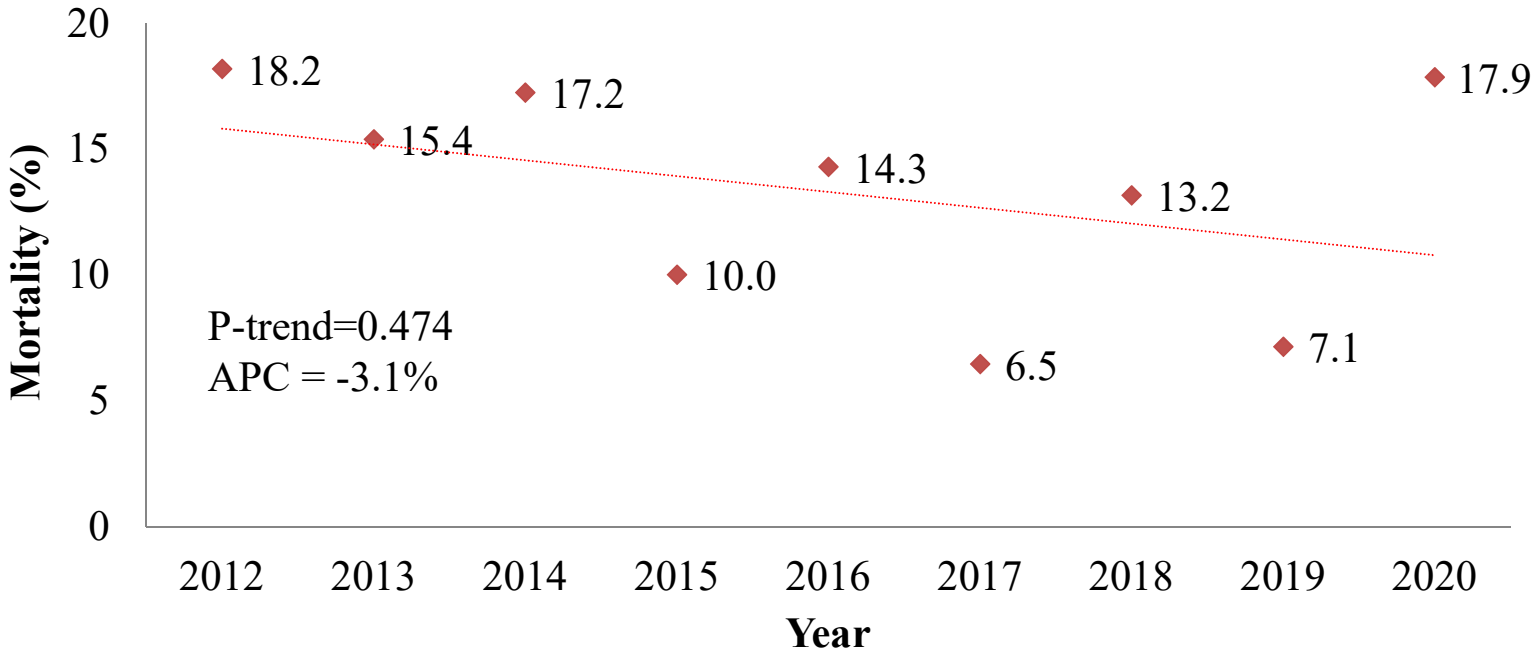
	2012	2013	2014	2015	2016	2017	2018	2019	2020
CRLM	38.1	52.2	42.3	32	32.1	40.7	33.3	37.9	32.1
PHCC	19	26.1	7.7	4	3.6	4.7	7.7	3.4	17.9
IHCC	19	13	26.9	12	25	22.2	23.1	24.1	17.9
HCC	23.8	8.7	23.1	52	39.3	33.3	35.9	34.5	32.1

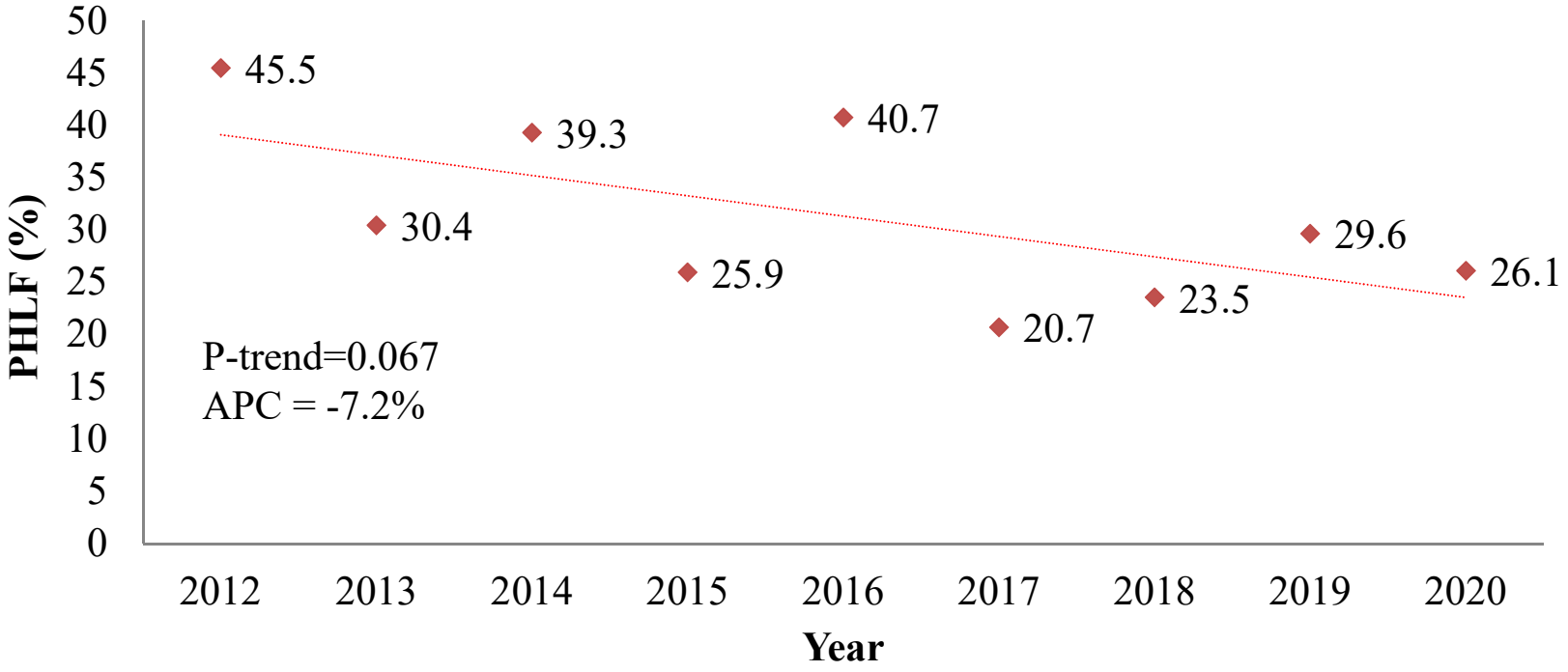


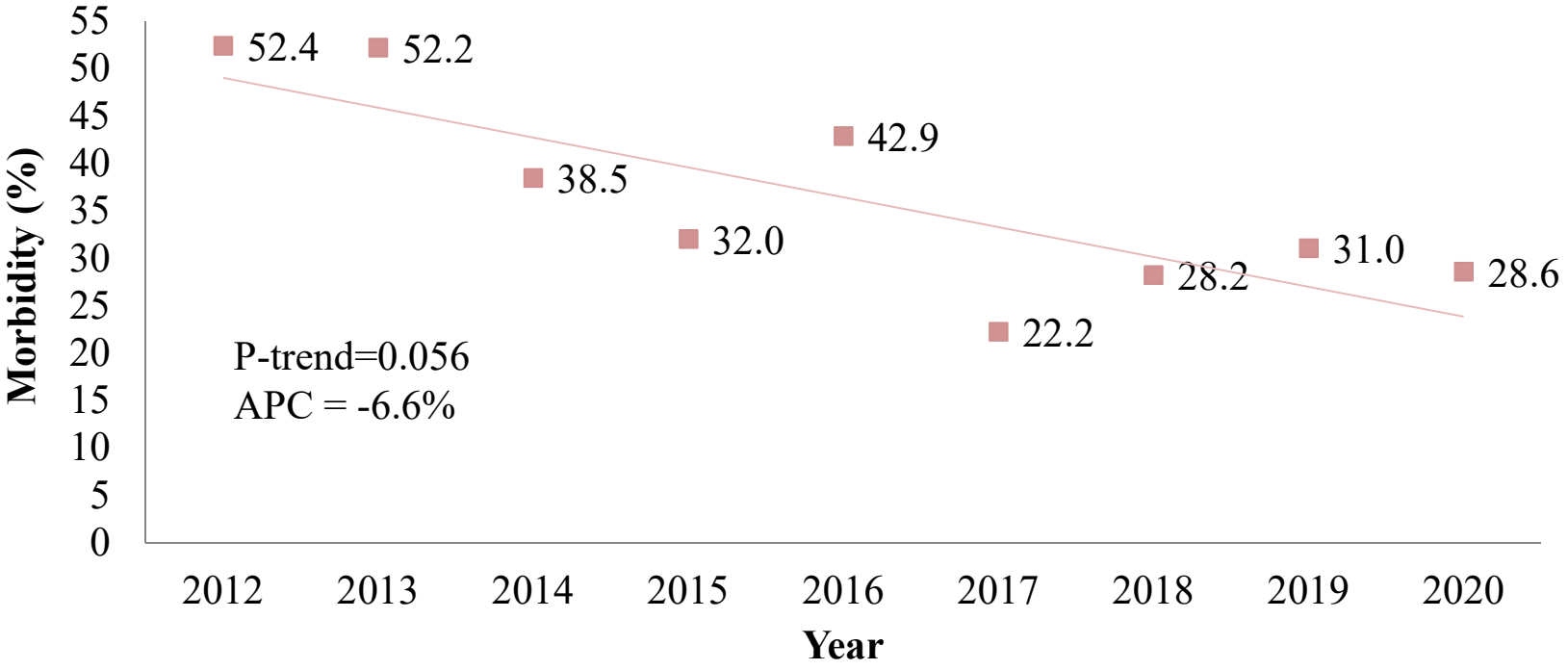
	2012	2013	2014	2015	2016	2017	2018	2019	2020
Robotic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.1	14.3
Laparo	0.0	0.0	0.0	3.3	21.4	6.5	23.7	42.9	35.7
Open	100.0	100.0	100.0	96.7	78.6	93.5	76.3	50.0	50.0



	2012	2013	2014	2015	2016	2017	2018	2019	2020
Robotic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.1	3.6
Laparo	0.0	0.0	0.0	0.0	3.7	3.4	21.1	25.0	28.6
Open	100.0	100.0	100.0	100.0	96.3	96.6	78.9	67.9	67.9


20
15
10
5
0
Mortality (%)
18.2
15.4
17.2
10.0
14.3
6.5
13.2
7.1
17.9
P-trend=0.474
APC = -3.1%
2012
2013
2014
2015
2016
2017
2018
2019
2020
Year


50
45
40
35
30
25
20
15
10
5
0
PHLF (%)
45.5
39.3
40.7
30.4
25.9
20.7
23.5
29.6
26.1
P-trend=0.067
APC = -7.2%
2012
2013
2014
2015
2016
2017
2018
2019
2020
Year


Morbidity (%)
55
50
45
40
35
30
25
20
15
10
5
0
52.4
52.2
42.9
38.5
32.0
22.2
28.2
31.0
28.6
P-trend=0.056
APC = -6.6%
2012
2013
2014
2015
2016
2017
2018
2019
2020
Year