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Could Impedance Cardiography be a Non-Invasive Alternative Method of Measuring Cardiac Output in Patients with Pulmonary Hypertension?

ABSTRACT

Background: Pulmonary hypertension guidelines recommend invasive right heart catheterization for diagnosis and clinical follow-up. Our aim was to compare non-invasive impedance cardiography with invasive techniques for cardiac index measurements and mortality prediction in patients with pulmonary hypertension.

Methods: Between 2008 and 2018, 284 right heart catheterizations were performed for the diagnosis of pulmonary hypertension in 215 patients with mean pulmonary artery pressure >25 mm Hg, and at least 2 methods used for cardiac output measurement were included in the study retrospectively. Patients were evaluated with Pearson's correlation in 3 groups: estimated Fick (eFick) method and thermodilution (group 1), eFick method and impedance cardiography (group 2), and thermodilution and impedance cardiography (group 3). We also compared the predictive power of cardiac index measured by different methods for 1-year overall mortality and hospitalizations.

Results: There were strong and moderate positive correlations in groups 1 and 3, respectively ($r=0.634$, $P<.001$, $r=0.534$, $P=.001$), and the weakest correlation was in group 2 ($r=0.390$, $P=.001$). The mean difference (bias) between eFick method versus impedance cardiography, impedance cardiography vs. thermodilution, and eFick method vs. thermodilution was 0.6 mL/min, 0.47 mL/min, and −0.2 mL/min respectively, but limits of agreement were wide. In both groups, cardiac index <2.5 L/min/m^2 as measured by thermodilution significantly predicted 1-year mortality. Also, impedance cardiography was better than eFick method in predicting mortality ($P=.02$).

Conclusions: Our single-center real-life data showed that for cardiac output and cardiac index measurements, impedance cardiography provides a moderate correlation with thermodilution and is fair with eFick method methods. Moreover, thermodilution appeared superior to both eFick method and impedance cardiography, while impedance cardiography was even better than eFick method in predicting 1-year adverse events, including total mortality and hospitalization, in patients with pulmonary hypertension.

Keywords: Hemodynamics, impedance cardiography, mortality, noninvasive assessment, pulmonary circulation and right ventricular

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INTRODUCTION

Current guidelines recommend right heart catheterization (RHC) and invasive cardiac output (CO) measurement for the diagnosis and clinical follow-up of patients with pulmonary hypertension (PH).[1] Cardiac output can be measured invasively during RHC using either the thermodilution (TD) method or the direct (d)-estimated(e) Fick method (dFick-eFick), as well as non-invasive impedance cardiography (ICG).[2] There is a lack of evidence for routine clinical use of non-invasive measurements of CO with ICG in PH.[3] Although there are some validation studies comparing TD with ICG, or directly with Fick and ICG, there are no studies evaluating the consistency of these 3 methods in terms of CO measurement in patients with PH. The purpose of our study was to compare eFick and TD techniques with ICG for CO measurement in patients with PH. We also aimed to compare the predictive value of these methods for 1-year overall mortality and

cardiovascular (CV) hospitalizations in patients with precapillary PH.

METHODS

All adult patients who had undergone RHC for the diagnosis of PH from January 2008 to January 2018 at Ege University Medical Faculty, Department of Cardiology were retrospectively screened. In order to be eligible for the study, patients should have had a mean pulmonary artery pressure (mPAP) of >25 mm Hg, and CO is measured simultaneously by at least 2 of the 3 methods (eFick, TD, and ICG), during the same RHC session. Exclusion criteria included unstable patient status (shock, hypotension, and arrhythmia disrupting hemodynamics), severe aortic valve regurgitation, and/or aortic stenosis. In addition, the TD method was excluded in patients with intra-and extracardiac shuts with a pulmonary cardiac output (Qp) to the systemic cardiac output (Qs) flow ratio >1 (Qp/Qs>1). The study protocol was approved by the Institutional Review Board (E.260895-18.09.2018).

Patients were grouped according to the methods used for the CO measurement; Group 1 covered patients who have been measured with both eFick and TD methods, group 2 covered patients who have been measured with both eFick and ICG, and group 3 covered patients who have been measured with both TD and ICG (group 3) measurement in the same RHC session. The measurement methods used in each group were compared in terms of correlation and agreement. To determine the clinical impact of the observed correlations, we also compared the predictive power of the cardiac index (CI) values measured by different methods for 1-year overall mortality and CV hospitalizations.

Cardiac Output Measurements and Right Heart Catheterization

All measurements were performed in the same RHC procedure by the same experienced investigator (H.K.) with a very low intra-observer variability. If a patient had a history of multiple RHCs during the study period, then the first RHC records were included in the study analysis. All RHC procedures and measurements were conducted by a Swan-Ganz or Cournand catheter placed in the pulmonary artery under fluoroscopy via the femoral vein. All pressure measurements including pulmonary capillary wedge pressure, pulmonary artery, right ventricular, and right atrium were recorded at the end of the expiration. Cardiac output was also measured by the following methods:

1. The eFick method, which uses the estimated oxygen consumption (VO_2) prepared according to age, height, weight, and gender, was used.[4] Simultaneous blood samples were received from both the systemic and pulmonary arteries and evaluated in the same blood gas analyzer.
2. The thermodilution technique was performed with 5 mL of cold injectate isotonic saline (0.9%). Five times of injection was given at the same rate from the proximal lumen of the Swan–Ganz catheter. The results of 15% over or under the mean obtained measurements were excluded and the average of at least 3 acceptable measurements was used.
3. An ICG device (NICCOMO, Medis, Medizinische Messtechnik GmbH, and Ilmenau, Germany) was used for ICG–CO measurements with arterial compliance modulation technique. Impedance cardiography measurements were obtained via electrodes placed on the bilateral jugular and lateral thoracic regions as described in the operation manual of the device.[5] Eight electrodes were placed on the patient's neck and thorax. Four current electrodes were used to pass a very low constant and alternating current (1.5 mA, 86 kHz) through the thorax, which was insensible and did not cause any physiological reaction. The voltage produced was measured.

Definitions

Pulmonary hypertension was diagnosed with mPAP of 25 mm Hg or above measured during the RHC at rest (defined by the 2015 ESC/ERS guidelines).[6] Cardiac index was calculated by dividing CO by the body surface area. The CI of ≥2.5 L/min/m^2 was accepted as the cutoff value for predicting good clinical status in PH patients.[7]

Overall mortality was defined as the rate of death from all causes for the study population during the 1-year follow-up period. Death due to worsening of the disease and sudden cardiac death were included as mortality data. Mortality information was retrieved from hospital records and national death information online data systems. Cardiovascular hospitalizations due to clinical worsening, right heart failure, syncope, and arrhythmia were also recorded.

Statistical Analysis

Quantitative data were expressed as mean ± SD according to the normal distribution, while categorical data were expressed as n (%). Normality was evaluated using the Kolmogorov–Smirnov test. Pearson's correlation analysis was used to evaluate the correlation of the CO measurement methods with each other, while Bland–Altman analysis was conducted to evaluate the agreement between the methods. With this analysis, the mean difference (bias) between the measurement methods and (±1.96 SD) upper and lower limits of agreement were evaluated. If the differences in the

HIGHLIGHTS

- Cardiac index measured during right heart catheterization in patients with the diagnosis of pulmonary hypertension is an important marker for determining the clinical prognosis.
- Thermodilution appeared superior to both estimated(e) Fick method and impedance cardiography, while impedance cardiography was even better than estimated(e) Fick method in predicting 1-year adverse events, including total mortality and hospitalization.
- Bland–Altman analysis showed that these tests were not interchangeable.
- Therefore, hemodynamic assessment with impedance cardiography might be used as a non-invasive, low-cost, easy prognostic predictor of survival in patients with pulmonary hypertension.

results were within mean ± 1.96 SD and these values were not clinically important, evaluated methods were accepted to be used interchangeably. Each test was compared for its predictive power of 1-year overall mortality and CV hospitalizations within the pairwise comparison group with Kaplan–Meier survival analysis. We also evaluated the correlation data using the *P*-value calculator for the correlation coefficients method which allowed us to obtain the corresponding *P*-values. All statistical analyses were conducted using SPSS (v.21) statistical package program and Medcalc (v.19) for Bland–Altman Test.

RESULTS

A total of 284 RHCs were performed between January 2008 and January 2018 with an initial diagnosis of PH in our center. Among these patients, 215 patients (mean age 52.8 ± 16.1 years, females 69.3%) with an mPAP value of >25 mm Hg in whom at least 2 methods were used for CO measurement were included in the study. Most of the study population either had group 1 PH (58.6%) or group 4 PH (chronic thromboembolic pulmonary hypertension) (17.7%) as PH etiology. Almost one-third (33%) of the group 1 PH had idiopathic pulmonary arterial hypertension. Considering the simultaneous catheter measurement groups, eFick and TD methods were used in 145 patients, eFick and ICG methods were used in 65 patients, and TD and ICG methods were used in 39 patients. Baseline clinical characteristics of the study population and groups are depicted in Table 1. In addition, the left ventricular ejection fraction was 56% (54.67-57.29) without making a significant difference in the groups, and similarly, the right ventricular ejection fraction was normal in 60% of the groups and mildly depressed in approximately 30%.

The evaluation of the paired comparisons of calculated CO and CI revealed that values measured by TD were higher than those of eFick and ICG. Bivariate Pearson correlation analysis revealed significant correlations among the variables. The CI obtained with the eFick method exhibited a strong positive correlation with TD ($r = 0.634$, $P < 0.001$), while TD and ICG showed a moderate positive correlation ($r = 0.534$, $P = .001$). The weakest correlation was observed between eFick and ICG ($r = 0.390$, $P = .001$). The measurements obtained from binary groups were evaluated with Bland–Altman analyses for agreement between different measurement methods (Figure 1). When we compared the significance of the correlation coefficients between the groups, the eFick–TD coefficient was statistically better than the eFick–ICG coefficient ($P = .0027$). No statistically significant difference was found between the TD–ICG correlation coefficient and the TD–eFick correlation coefficients ($P = .414$). Additionally, there was no significant difference observed between ICG–eFick correlation coefficient and ICG–TD correlation coefficient ($P = .380$). These findings further indicate that the weakest relationship exists between eFick and ICG.

A comparison of CI measurement values is shown in Table 2. In between-group assessments, the mean difference in measurement with eFick and TD in group 1 was 0.2 L/min/m^2. In general, the CI measurements conducted by TD were higher than those measured by the eFick method. Ninety-five percent limits of agreement were observed in the range of −1.7 to 1.2 and the error percent was 45.2%. Comparisons were made between eFick and ICG in Group 2, and ICG showed lower measurement results overall. The average difference was 0.6 L/min/m^2, and 95% limits of agreement were in the range of −1.6 to 2.7 with an error percent of 67.32%. In Group 3, where TD and ICG were compared, the mean difference was 0.47 L/min/m^2, with a 95% agreement limit of −0.84 to 1.78 and an error percentage of 42.4%.

The mean follow-up was 31 ± 26 months for the study population. The CI values less than 2.5 L/min/m^2 measured by TD in both groups significantly predicted the 1-year mortality (Group 1 eFick vs. TD: $P = .013$ and Group 3 TD vs. ICG: $P = .040$, respectively) (Table 3). However, CI measured by eFick method failed to predict mortality either in the group compared with TD or in group 3 compared with ICG. The CI measured by ICG, on the other hand, significantly predicted 1-year mortality compared to eFick ($P = .02$). However, ICG–CI remained at the borderline significantly compared with TD ($P = .052$) (Figure 2).

DISCUSSION

Cardiac output and CI measured during RHC in patients with the diagnosis of PH are important markers for determining the clinical prognosis and guiding the treatment.[1] Though current guidelines recommend[1] direct Fick and TD methods for the determination of CO in PH patients, the invasive, time-consuming, and hospital-based nature of these techniques prohibit their use in daily workups and routine follow-up. We report on the reliability of a noninvasive and simple method of assessing CO and CI using ICG in patients with PH. In our study, although the invasive TD and eFick methods and the non-invasive ICG showed consistent results with each other, they showed fair precision in terms of good accuracy agreement. But the limits of agreements of the tests were large which probably denote the non-interchangeability between the tests. We also showed that ICG measured CI was superior to both TD and eFick in predicting 1-year adverse events including overall mortality and hospitalizations (group 1 eFick vs. TD 42.8%, group 2 eFick vs. ICG 27.7%, and group 3 TD vs. ICG 74.4%, respectively, Table 1). To the best of our knowledge, our study is the first comparison of the 3 methods in terms of accuracy, precision, and mortality prediction in routine practice in patients with PH.

It is well known that all methods used for CO measurement have certain limitations. The available literature mainly focuses on the comparison of dFick and TD in general. Most of the previous studies comparing these methods have previously included selected small groups of patients who followed strict study protocols.[3,5,8,9] Opotowsky et al[9] reported a moderate correlation ($r = 0.65$) between the TD and eFick methods for CI measurement in a retrospective analysis of >12 000 patients with heart failure who underwent RHC. However, their Bland–Altman analyses revealed that there was no good acuity between these 2 CI measurement methods in terms of accuracy due to the high limits of the agreement values [mean difference −0.002 L/min/m^2, limits of

Table 1. Clinical Characteristics of the Study Groups

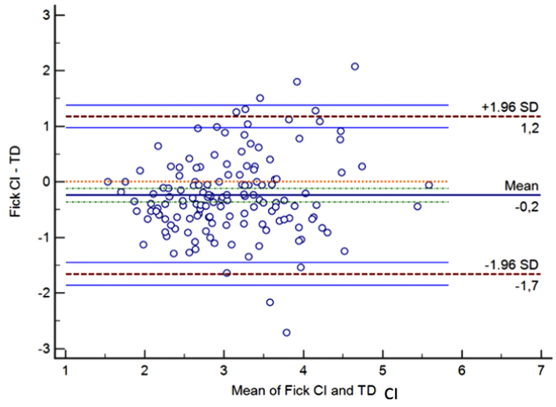
	All Patients (n = 215)	Group 1 eFick-TD (n = 145)	Group 2 eFick-ICG (n = 65)	Group 3 TD-ICG (n = 39)
Age (years)	52.8 ± 16.1	54.8 ± 14.8	47.24 ± 16.1	51.46 ± 14.7
Gender, Female (%)	149 (69.3)	93 (64.1)	43 (66.2)	23 (59.0)
BSA	1.76 ± 0.22	1.79 ± 0.21	1.74 ± 0.22	1.83 ± 0.19
WHO-FC				
1	13 (6.1)	6 (42.2)	7 (10.8)	2 (5.2)
2	120 (55.8)	85 (58.6)	28 (58.4)	25 (64.1)
3	77 (35.8)	52 (35.8)	20 (30.8)	12 (30.7)
4	5 (2.3)	2 (1.4)	0	0
PH group				
1	126(58.6)	78 (53.8)	44 (67.7)	21 (53.8)
2	24 (11.2)	13 (9)	6 (9.2)	4 (10.3)
3	24 (11.2)	17 (11.7)	1 (1.5)	1 (2.6)
4	38 (17.7)	34 (23.4)	14 (21.5)	13 (33.3)
5	3 (1.4)	3 (2.1)	0	0
Comorbidities (%)	90 (41.9)	67 (46.2)	23 (35.4)	20 (51.3)
HT	41 (19.1)	32 (22.1)	13 (20)	13 (33.3)
DM	21 (9.8)	16 (11)	1 (1.5)	0
CRF	6 (2.8)	5 (3.4)	0	0
AF	22 (10.2)	14 (9.7)	9 (13.8)	7 (17.9)
PAH-specific treatment (%)	124 (53.7)	86 (59.2)	39 (60)	26 (66.7)
1-Year mortality (%)	40 (18.6)	33 (22.8)	9 (13.8)	8 (20.5)
1-Year mortality and CV hospitalization (%)	82 (38.1)	62 (42.8)	18 (27.7)	29 (74.4)
Overall mortality (%)	92 (42.8)	76 (52.4)	30 (46.2)	20 (51.3)
Hemodynamic evaluation				
sPAP	74.5 ± 24.7	71.3 ± 23.1	80.7 ± 28.7	75.4 ± 26.7
mPAP	47.2 ± 15.4	45.71 ± 13.9	51.03 ± 18.63	45.51 ± 15.9
CO (eFick) (L/min)	5.28 ± 1.73	5.31 ± 1.61	5.56 ± 2.01	–
CO (TD) (L/min)	5.73 ± 1.42	5.73 ± 1.42	–	5.68 ± 1.38
CO (ICG)	4.60 ± 1.44	–	4.60 ± 1.44	4.83 ± 1.45
CI (eFick) (L/min/m^2)	3 ± 0.97	2.97 ± 0.87	3.19 ± 1.13	–
CI (TD) (L/min/m^2)	3.21 ± 0.78	3.21 ± 078	–	3.09 ± 072
CI (ICG)	2.61 ± 0.70	–	2.61 ± 0.69	2.61 ± 0.71

AF, atrial fibrillation; BSA, body surface area; CO, cardiac output; CI, cardiac index; CRF, chronic renal failure; CV, cardiovascular; DM, diabetes mellitus; HT, hypertension; ICG, impedance cardiography; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; sPAP, systolic pulmonary arterial pressure; TD, thermodilution; WHO-FC, World Health Organization functional class.

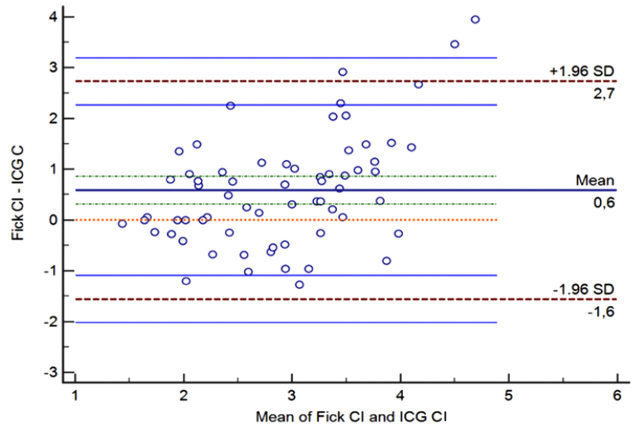
agreement (LOA): −1.3 to +1.3 L/min/m^2].[9] However, only half of 56.4% of their patient population had PH.

There are limited number of studies comparing ICG with dFick or TD methods in patients with PH.[3,5,8,10,11] Tonelli et al[10] compared the CO results measured by ICG and TD methods in 39 patients who underwent RHC with the suspicion of PH (only 30 patients were diagnosed with PH), and the correlation between the measurements was good ($r = 0.7$, $P = .001$), while the mean difference was 0.3 L/min, and the limits of agreement in Bland–Altman analysis was −2.2 to +2.8 which clinically meant that the correlation between ICG and TD was good but the agreement was poor.[10] Yung et al[11] also reported very good binary correlations between invasive and non-invasive methods measuring CO in 42 PH patients ($r = 0.84$ for ICG and dFick, $r = 0.80$ for ICG and TD, and $r = 0.89$ for TD and dFick).

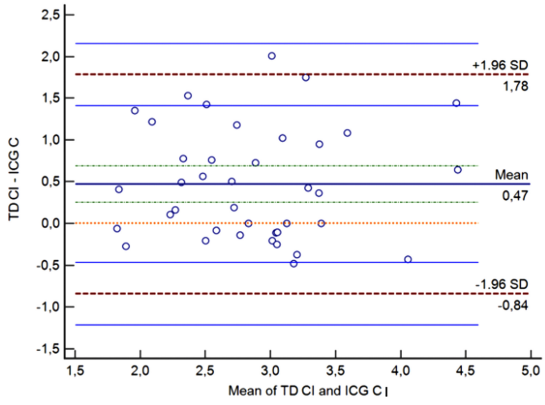
In our study, though the measurements in the eFick and TD comparison group showed a good correlation ($r = 0.634$ $P = .001$), the mean difference of the CI measured with the TD method was 0.2 L/min/m^2 higher than the eFick method, and the limits of agreement values were too high to indicate a good precision. This discrepancy is probably due to the VO_2 estimation method used for the eFick, as in other studies using eFick. In the direct Fick method, oxygen consumption is evaluated directly via a facemask, while in the eFick method, oxygen consumption tables prepared according to gender, height, weight, and heart rate are used. The eFick method is generally preferred in daily practice since



A: eFick CI- TD CI Bland Altman.



B: eFick CI- ICG CI Bland Altman



C: TD CI – ICG CI Bland Altman

Figure 1. Bland–Altman analyses with the measurements obtained from binary groups. Bland–Altman graphics for 3 methods (A) group 1, eFick and TD CI, (B) group 2, eFick and ICG, and (C) group 3, TD CI–ICG CI. CI, cardiac index; ICG, impedance cardiography; SD, standard deviation; TD, thermodilution.

direct measurement of oxygen consumption needs an additional medical device, cost, and time during catheterization. However, Narang et al[12] have reported more than a 25% difference between the VO_2 values measured directly and estimated according to the formulas in 25% of the patients. Likewise, this difference could be more pronounced in patients with PH. Therefore, the moderate correlation and fair precision we observed between the eFick and ICG methods in patients' PH could be explained by this fact. Moreover, the lower values we observed for CI measurements by TD and ICG than the findings of Tonelli et al[10] and Yung et al[11] might be due to our study populations' characteristics, i.e., solely consisting of PH patients and larger sample size. Of note, unlike previous studies, all our patients were diagnosed with PH.

Table 2. Comparison of Cardiac Index Measurement Values Within Groups

		CI bias	Limits of Agreement	Percentage Error (%)
eFick CI vs. TD CI	0.634	−0.2	1.2-1.7	45.2
eFick CI vs. ICG CI	0.390	0.6	2.7-1.6	67.3
TD CI vs. ICG CI	0.564	0.47	1.78-0.84	42.4

Bland–Altman analysis was used to measure the agreement between variables. CI, cardiac index; ICG, impedance cardiography; TD, thermodilution.

Another important statistical parameter used in comparing the results of a new method with the reference method is percentage error.[13] A percentage error <30%, which is by Odor et al[14] indicates that the correlation of the methods is within clinically acceptable limits. None of the comparison groups in the current study had a percentage error <30% (45.2%, 67.3%, and 42.4%, respectively). These results also support the fair precision between measurement methods.

The PH guidelines state that CI >2.5 L/min/ m^2 is associated with good clinical outcomes.[1] However, there is no clear suggestion on which CI measuring value should be taken as a reference.[15] In a retrospective analysis of patients with heart failure, TD and eFick methods were compared with reference to a value of 2.2 L/min/m^2, and although both methods could predict 1-year mortality, TD was shown to be a better predictor of mortality.[16] Since PH patients were examined

Table 3. Evaluation of 1-Year Overall Mortality and Cardiovascular Hospitalizations According to Intergroup Cardiac Index Values

	Group 1 eFick CI–TD CI		Group 2 eFick CI–ICG CI		Group 3 TD CI–ICG CI	
	eFick CI < 2.5	TD CI < 2.5	Fick CI < 2.5	ICG CI < 2.5	TD CI < 2.5	ICG CI < 2.5
1-Year mortality	0.109	0.013	0.064	0.020	0.040	0.052
95% CI	9.888-11.229	10.057-11.219	10.956-11.977	10.871-12.182	9.781-11.795	10.072-12.292
1-Year mortality–CV	0.959	0.036	0.120	0.041	0.054	0.09
Hospitalizations 95% CI	7.634-9.502	8.12-9.719	9.423-11.377	9.811-11.715	8.186-11.026	8.813-11.732

The effects of the methods used on survival were examined using the log-rank test. The Kaplan–Meier survival estimates were calculated. CI, cardiac index; CV, cardiovascular; ICG, impedance cardiography; TD, thermodilution.

in this study, a comparison was made with reference to the 2.5 L/min/m^2 value predicted in the guidelines, and TD predicted mortality significantly in the groups in which it was compared with both eFick and ICG (P = .020; 95% CI 1.6-2.7), whereas eFick was unable to estimate 1-year mortality. The main reason for these results is probably due to the estimated VO_2 acceptance in eFick. Considering this result and the mean difference determined in the Bland–Altman analysis, we think that there is a need for a different reference for eFick, considering that lower results are obtained in the eFick method compared to TD. Mortality was found to be significantly lower in the group with eFick in the ICG measurement in terms of mortality over 2.5 L/min/ m^2 (P = .020), while the P-value was borderline in the group encountered with TD. Here, the low number of patients in the TD–ICG group might be the cause.

Strengths and Limitations

The retrospective nature of the study might be accepted as a major limitation of our study. However, our findings represent real-life data from an experienced PH center where all invasive hemodynamic measurements were conducted by the same investigator. Second, the study sample size was relatively small as it was generated from a single center. The heterogeneity of the groups regarding PH etiologies might also be regarded as a limitation. The lack of comparison of the patient groups in terms of the causes of PH and treatment might also be considered a limitation. However, our protocol

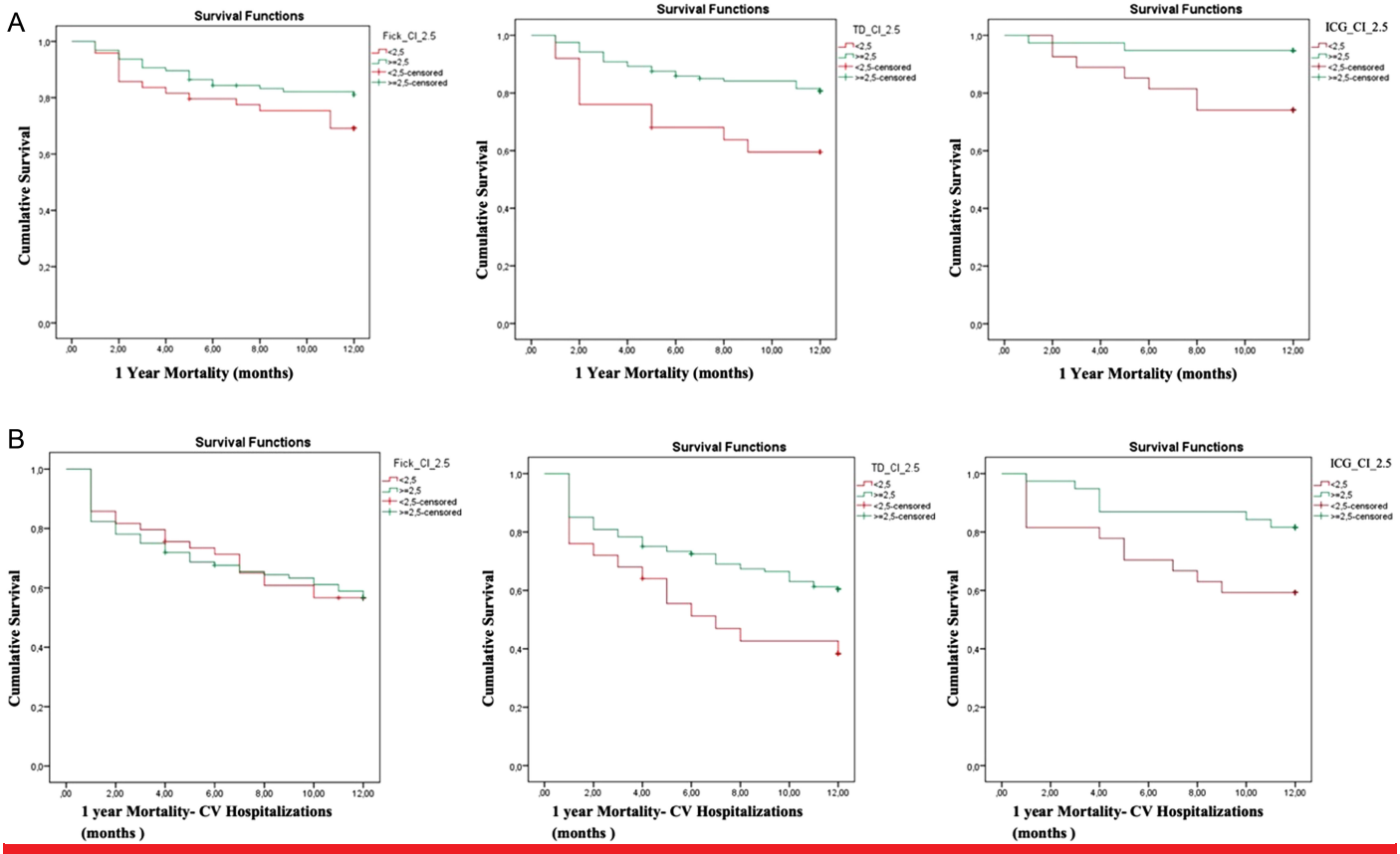


Figure 2. Kaplan–Meier analysis for 1-year mortality (A) and 1-year mortality and cardiovascular hospitalizations (B) according to the 3 different methods. CI, cardiac index; CV, cardiovascular; ICG, impedance cardiography; TD, thermodilution.

was planned to compare the CI measurement methods within groups, not between patient groups. Therefore, any difference between the patient will not affect the comparison of the methods. Additionally, major CV risk factors such as diabetes, hypertension, coronary artery disease, accompanying major comorbidities, and parameters that could predict mortality such as both left and right ventricular systolic functions were not stated as they were not statistically different between the groups.

Another aspect of our study was that most of our study population was consisting of PH patients with WHO functional classes 2 and 3. Therefore, our results might not be generalized especially to those patients with functional class 4. The value of ICG in patients with advanced functional class PH may not be interpreted with our results. Despite all these facts, our study is the first comparison of the 3 methods in terms of mortality prediction in routine practice in patients with PH.

CONCLUSION

The present single-center real-life data showed that for CO and CI measurements, ICG is moderately correlated with TD and fairly with eFick methods. Thermodilution seems to be superior to both eFick and ICG, whereas ICG is superior to eFick for predicting 1-year adverse events including overall mortality and hospitalizations in patients with PH. These results may imply that hemodynamic assessment with ICG might be used as a non-invasive, low-cost, easy prognostic predictor of survival in patients with PH. Though larger studies covering all PH subgroups are warranted, ICG seems to provide non-invasive continuous hemodynamic follow-up of patients with PH.

Ethics Committee Approval: This study was approved by Ethics Committee of Ege University (Decision Date and Decision Number: 18.09.2018-E.260895).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.Y., E.Ş.; Design – E.Ş., M.K.; Supervision – M.K., H.K.; Resources – B.Y., E.İ.Y.E.; Materials – E.İ.Y.E, Y.B.C.; Data Collection and/or Processing – B.Y., Y.B.C.; Analysis and/or Interpretation – E.Ş., M.K.; Literature Search – B.Y., E.Ş.; Writing – B.Y., M.K.; Critical Review – M.K., S.N., N.M., H.K.

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