Relation of Body Mass Index to Outcomes in Patients With Heart Failure Implanted With Left Ventricular Assist Devices

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We aimed at characterizing the impact of low and high body mass index (BMI) on outcomes after left-ventricular assist device (LVAD) surgery and define the predictors of mortality in patients with abnormal BMI (low/high). This study was conducted in 19 centers from 2006 to 2016. Patients were divided based on their baseline BMI into 3 groups of BMI: low (BMI ≤18.5 kg/m^2); normal (BMI = 18.5 to 24.99 kg/m^2) and high (BMI ≥25 kg/m^2) (including overweight (BMI = 25 to 29.99 kg/m^2), and obesity (BMI ≥30 Kg/m^2)). Among 652 patients, 29 (4.4%), 279 (42.8%) and 344 (52.8%) had a low-, normal-, and high BMI, respectively. Patients with high BMI were significantly more likely men, with more co-morbidities and more history of ventricular/supra-ventricular arrhythmias before LVAD implantation. Patients with abnormal BMI had significantly lower survival than those with normal BMI. Notably, those with low BMI experienced the worst survival whereas overweight or obese patients had similar survival. Four predictors of mortality for LVAD candidates with abnormal BMI were defined: total bilirubin ≥16 μmol/L before LVAD, hypertension, destination therapy, and cardiac surgery with LVAD. Depending on the number of predictor per patients, those with abnormal BMI may be divided in 3 groups of 1-year mortality risk, i.e., low (0 to 1 predictor: 29% and 31%), intermediate (2 to 3 predictors, 51% and 52%, respectively), and high (4 predictors: 83%). In conclusion, LVAD recipients with abnormal BMI experience lower survival, especially underweight patients. Four predictors of mortality have been identified for LVAD population with abnormal BMI, differentiating those a low-, intermediate-, and high risks of death. **(Am J Cardiol 2020;133:81−88)**

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Left ventricular assist device (LVAD) implantation has been shown to improve survival in patients with refractory heart failure (HF).[1−3] However, an optimal LVAD candidate selection is crucial to expect favorable outcomes after pump implantation. It has been well established that obesity increases the morbidity and mortality in patients scheduled for cardiac surgery.[4] Conversely, the impact of body mass index (BMI) on outcomes after LVAD implantation seems unclear. Indeed, previous published works did not observe that obesity or extreme obesity were associated with higher mortality among the LVAD population[5−9] but may predispose to an increased rate of adverse events.[5,8,10] In opposite, limited data have shown that small body size was correlated with higher mortality in LVAD recipients,[11,12] whereas a larger study observed that low BMI did not impact the survival in patients with LVAD.[9] In this large multicenter cohort, we aimed at better characterizing the impact of low- and high BMI on outcomes after LVAD surgery and define the predictors of overall mortality in patients with abnormal BMI (low or high) scheduled for LVAD implantation.

Methods

The ASSIST-ICD (Clinicaltrials.gov identifier: NCT02873169) is a retrospective, multicenter observational study of durable mechanical circulatory support devices implanted in patients treated in 19 tertiary care centers in France. The study methods have been previously reported.[13] Briefly, patients aged ≥18 years implanted with axial HeartMate 2 (Abbott, Chicago, Illinois), Jarvik 2000 (Jarvik Heart, Inc., New York, New York) or centrifugal HeartWare (Medtronic, Minneapolis, Minnesota) pumps from February 2006 to December 2016 were included. Exclusion criteria were total artificial heart placement or pulsatile flow LVAD, history of heart transplant, and receipt of a VentrAssist device (Ventracor, Chatswood, NSW, Australia). This study was approved by the regional ethics committees, the French Advisory Committee on the Treatment of Research Information in the Field of Health, and the French National Commission of Informatics and Civil Liberties. A nonopposition letter was sent to the patients, as requested by French authorities for retrospective studies.

Baseline data − including demographic characteristics, cardiac disease, and heart failure history, echocardiography − were collected from hospital files for all patients. Perioperative data (such as the necessity of a combined surgery) were also collected.

Follow-up was performed according to each institution's protocols. The LVAD controller monitor was checked during every clinical visit in each center, according to the state-of-the-art standard of care for LVAD recipients. The last day of follow-up was December 31, 2016, the date of heart transplantation, or death, whichever occurred first.

For the purpose of this study, the overall population was divided based on their baseline BMI into 3 groups: low (BMI ≤18.5 kg/m^2); normal (BMI: 18.5 to 24.99 kg/m^2) and high (BMI ≥25 kg/m^2) BMI (including overweight (BMI: 25 to 29.99 kg/m^2), and obese (BMI ≥30 Kg/m^2) patients). Of note, patients were grouped according to BMI based on the World Health Organization classification.[14]

The primary end point of the study was all-cause mortality. Deaths were classified as cardiovascular death (cardiac or vascular cause), noncardiac death, or unknown cause. Secondary end points included heart transplantation and LVAD related complications (i.e., thrombosis, stroke, bleeding, driveline infection, or pump replacement).

Normally distributed variables were expressed as means ± SD and compared using Student's *t* test. Non-normally distributed variables were expressed as median and interquartile ranges and compared using Mann-Whitney's *U* test. Categorical variables were expressed as counts and percentages and were compared using the chi-square test or exact Fisher test when needed. Differences between groups were quantified by using ANOVA and chi-square tests when appropriate. Survival analysis was performed using Kaplan−Meier estimates, and log-rank tests were used to compare groups. A p value <0.05 was considered statistically significant. The optimal cut-off values were defined using receiver-operating characteristic curves and the maximum Youden's index (sensitivity + specificity). Predictors of mortality were analyzed using univariate and multivariable proportional hazard models. The proportional hazard assumption was tested and verified for each covariate. Variables with p values <0.05 in univariate analysis were included in the multivariable analysis. The analyses were performed with the SPSS statistical package, version 11.0 (SPSS Inc., Chicago, IL).

Results

From 2006 to 2016, a total of 659 patients were implanted with a continuous-flow LVAD and included in the study. Among these, 7 patients were excluded (3 patients received a VentrAssist and 4 patients died during the LVAD surgery). A total of 652 patients were included in the final analysis and followed during 9.1 (2.5 to 22.1) months. Among this population, a total of 29 (4.4%), 279 (42.8%) and 344 (52.8%) patients were classified in the low-, normal-, and high BMI groups, respectively. Of note, in the high BMI group, 241 (37.0%) patients were overweight with a BMI ranging from 25 to 29.99 kg/m^2 and 103 (15.8%) were obese with a BMI ≥30 kg/m^2. The description of the study population depending on the BMI is represented in Figure 1. The baseline characteristics of the 3 groups are detailed in Table 1. Patients with high BMI (i.e., ≥25 kg/m^2) were significantly more likely men, with more co-morbidities and more history of ventricular/supra-ventricular arrhythmias before LVAD implantation. Conversely, those with normal BMI had shorter HF duration with less dilated left ventricle and were less likely to receive optimal HF drugs before LVAD surgery compared with the LVAD recipients with non-normal BMI.

Interestingly, patients with abnormal BMI (i.e., low- and high groups) experienced a significantly longer stay in ICU compared with those with normal BMI. However, no difference was found regarding total in hospital stay but patients with low BMI had a numerically longer total hospital stay (Table 1). During the study period, patients with low-, normal-, and high BMI had a similar rate of LVAD-related thrombosis, stroke, bleeding, and driveline infection. However, those with high BMI exhibited a nonsignificant trend

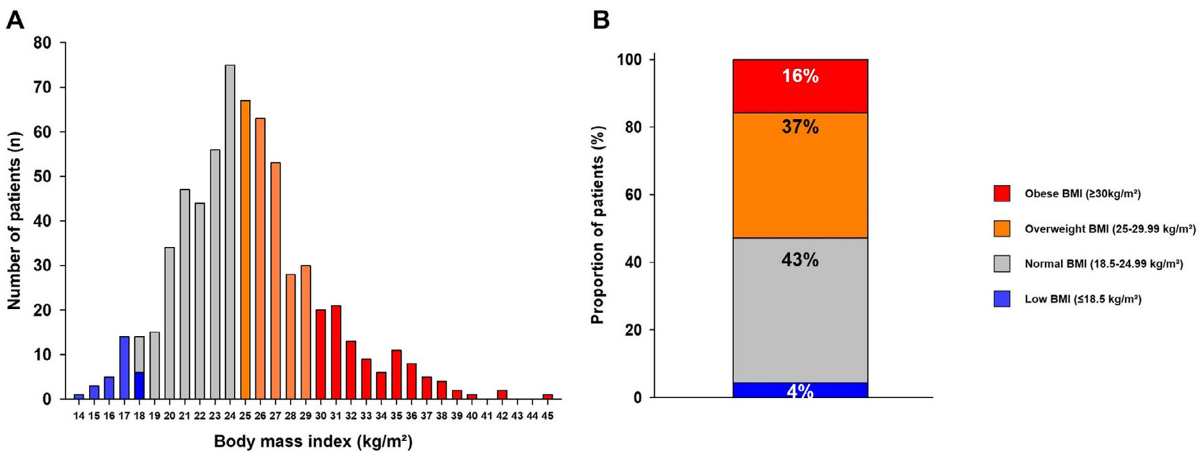


Figure 1. Proportion of LVAD recipients with abnormal BMI. *(A)*Number of patients depending on the BMI. *(B)*Proportion of patients depending on the BMI.

Table 1
Baseline characteristics between patients with low-, normal-, or high BMI

Variable	Body mass index ≤18.5 kg/m^2 (n = 29)	Body mass index 18.5-24.99 kg/m^2 (n = 279)	Body mass index ≥25 kg/m^2 (n = 344)	p Value
Age, (years)	58.2 (53.4-64.8)	59.8 (50.0-67.1)	59.9 (52.2-65.9)	0.831
Men	21 (72%)	233 (83%)	307 (89%)	**0.012**
Body mass index, (kg/m^2)	17.5 (16.8-17.8)	22.7 (21.2-24.1)	27.7 (26.2-30.7)	**<0.001**
Hypertension	9 (30%)	80 (29%)	144 (42%)	**0.002**
Diabetes mellitus	4 (14%)	52 (19%)	98 (28%)	**0.007**
Dyslipidemia*	6 (21%)	111 (40%)	166 (48%)	**0.004**
Smoker	16 (55%)	169 (61%)	210 (56%)	0.545
Heart failure etiology				0.234
-Ischemic	13 (45%)	180 (64%)	219 (64%)	
-Idiopathic	11 (38%)	71 (25%)	96 (28%)	
-Other	5 (17%)	28 (10%)	29 (8%)	
Heart failure duration, (months)	66.9 (5.1-137.2)	30.4 (1.1-154.2)	76.2 (4.7-176.2)	**0.006**
Ventricular arrhythmia	4 (14%)	81 (29%)	138 (40%)	**<0.001**
Supra-ventricular arrhythmia	9 (31%)	118 (42%)	175 (51%)	**0.025**
Left ventricular ejection fraction before LVAD, (%)	20.0 (13.7-25.0)	20.0 (15.0-25.0)	20.0 (15.0-25.0)	0.710
Left ventricular end-diastolic diameter before LVAD, (mm)	69.0 (60.0-72.0)	68.0 (62.0-72.2)	71.0 (65.0-77.0)	**<0.001**
Creatinine, (μmol/L)	105.0 (78.0-132.2)	112.0 (82.5-148.0)	119.0 (89.0-147.2)	0.202
Serum sodium, (mmol/L)	136.0 (131.7-139.0)	135.5 (132.0-139.0)	136.0 (132.0-139.0)	0.944
Total bilirubin, (μmol/L)	13.0 (9.5-23.3)	15.7 (10.0-27.0)	16.0 (11.0-27.0)	0.272
Drugs before LVAD implantation				
-Beta-blockers	18 (62%)	168 (60%)	237 (69%)	0.074
-Angiotensin converting enzyme inhibitors/angiotensin-receptor blockers	19 (65%)	164 (59%)	237 (69%)	**0.032**
-Mineralocorticoid receptor antagonist	19 (65%)	135 (48%)	202 (59%)	**0.017**
-Amiodarone	10 (34%)	119 (43%)	155 (45%)	0.502
Implantable cardioverter defibrillator prior to LVAD	13 (45%)	158 (56.6%)	232 (67%)	**0.003**
Cardiac resynchronization therapy prior to LVAD	6 (21%)	74 (26.5%)	118 (34%)	0.056
LVAD				0.477
-HeartMate II	18 (62%)	203 (73%)	254 (74%)	
-HeartWare	7 (24%)	58 (21%)	62 (18%)	
-Jarvik2000	4 (14%)	18 (6%)	28 (8%)	
Indication				0.980
-Bridge to transplantation	17 (59%)	162 (58%)	208 (60%)	
-Destination therapy	11 (38%)	109 (39%)	127 (37%)	
-Bridge to decision/recovery	1 (3%)	8 (3%)	9 (2%)	
Surgery combined with LVAD	5 (17%)	42 (15%)	48 (14%)	0.891
Temporary right extra corporeal life support during surgery	4 (14%)	29 (17%)	48 (14%)	0.520
Early ventricular arrhythmia (<30 days)	6 (21%)	54 (19%)	102 (30%)	**0.011**
Total days in intensive care unit	15.0 (12.0-42.7)	13.0 (8.0-23.0)	16.0 (10.030.0)	**0.025**
Total days in hospital	49.0 (32.0-82.5)	40.0 (28.0-57.0)	42.0 (31.0-58.2)	0.217

Bold p-value are for significant results (i.e. p<0.05).
* Dyslipidemia is defined as having a high plasma triglyceride concentration and/or a high plasma LDL cholesterol and/or a low HDL (protective) cholesterol.

Table 2
Outcomes between patients with low-, normal-, and high BMI

Variable	Body mass index ≤18.5 kg/m^2 (n = 29)	Body mass index 18.5-24.99 kg/m^2 (n = 279)	Body mass index ≥25 kg/m^2 (n = 344)	p Value
Total death	14 (48%)	105 (38%)	172 (50%)	**0.008**
Cause of death				0.052
-Cardiovascular	5 (36%)	39 (37%)	81 (47%)	
-Non-cardiovascular	9 (64%)	62 (59%)	91 (53%)	
-Unknown	0 (0%)	4 (5%)	0 (0%)	
Heart transplantation	7 (24%)	95 (34%)	97 (28%)	0.215
LVAD thrombosis	1 (3%)	31 (11%)	52 (15%)	0.100
Stroke	2 (7%)	34 (12%)	52 (15%)	0.322
Bleeding	7 (24%)	47 (17%)	58 (17%)	0.596
-Cerebral bleeding	4 (14%)	17 (6%)	15 (4%)	0.088
-Digestive bleeding	2 (7%)	18 (6%)	27 (8%)	0.797
-Subcutaneous	0 (0%)	3 (1%)	7 (2%)	0.494
-Other	1 (3%)	5 (1%)	13 (4%)	0.336
Percutaneous driveline infection	8 (28%)	78 (28%)	85 (25%)	0.648
LVAD replacement	0 (0%)	12 (4%)	21 (15%)	**<0.001**
Cause for LVAD replacement:				0.404
-LVAD thrombosis	-	8 (67%)	15 (71%)	
-LVAD dysfunction	-	3 (25%)	2 (9%)	
-Other	-	1 (8%)	4 (19%)	

Bold p-value are for significant results (i.e. $p<0.05$).

toward higher episode of thrombosis and stroke (Table 2). Conversely, those with low BMI presented numerically more cerebral bleeding event. Importantly, no pump replacement was performed in the low BMI group whereas 14.8% of the patients with high BMI had device exchange during the study period (p <0.001).

During a 9.1 (2.5 to 22.1) months follow-up, a total of 291 patients died, 14 (48.3%), 105 (37.6%), and 172 (50.0%) in the low-, normal-, and high BMI groups, respectively (p = 0.008). Additionally, there was a trend toward a higher cause of cardiac death in the group with high BMI and noncardiac death in the low BMI group. Last, although being nonsignificant, underweight patients were numerically less likely to receive heart transplantation during follow-up. As illustrated in Figure 2 patients with abnormal BMI had significantly lower survival than those with normal BMI. Interestingly, LVAD recipients with low BMI experienced the worst survival whereas overweight or obese patients had similar intermediate survival (Figure 2)

Multivariable analysis identified 4 significant predictors of overall mortality among the population with abnormal BMI scheduled for LVAD implantation: total bilirubin ≥16

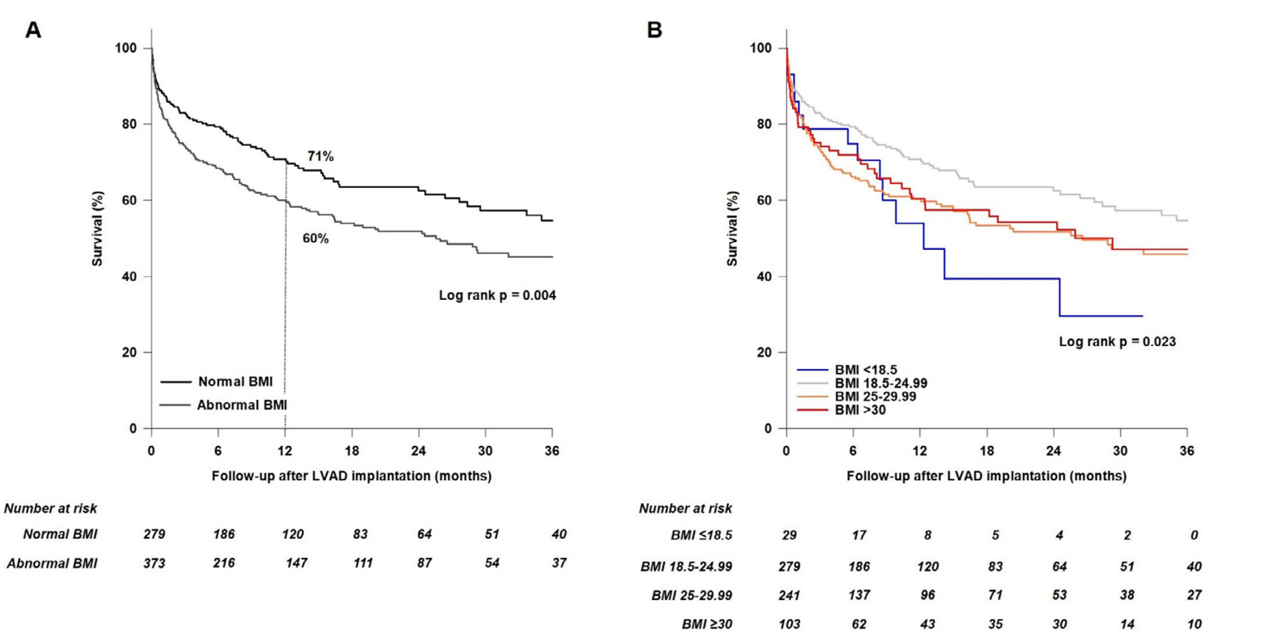


Figure 2. Survival curves. *(A)*Survival curves in patients with normal or abnormal BMI. *(B)*Survival curves between LVAD recipients with underweight, normal, overweight, and obese BMI.

Table 3
Multivariate analysis for the predictor of overall mortality in patients with abnormal BMI

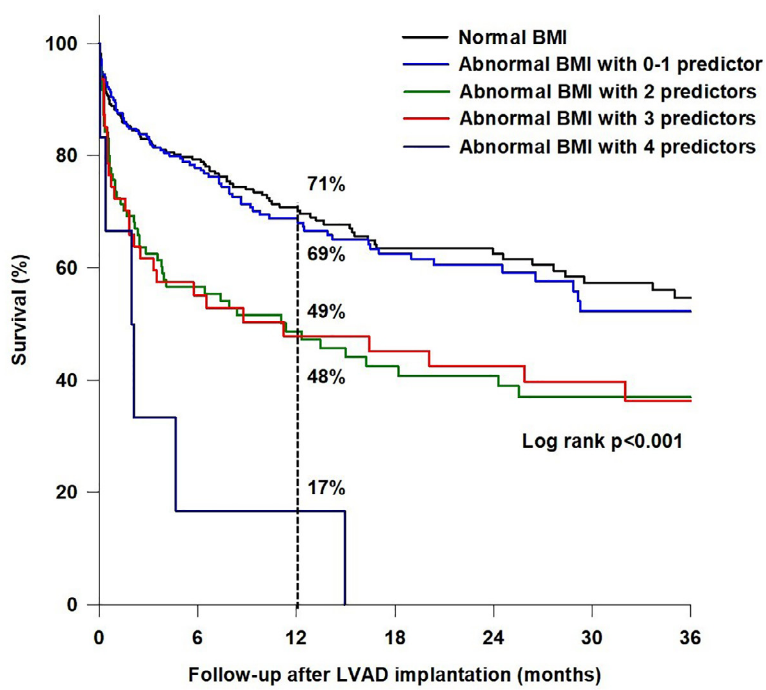
Variable	β coefficient	Multivariable HR (95%CI)	p Value
Age, (years)	0.005	1.01 (0.98-1.03)	0.727
Hypertension	0.572	1.77 (1.08-2.92)	**0.024**
Dyslipidemia	0.337	1.40 (0.85-2.30)	0.183
Total bilirubin ≥16 μmol/L	0.571	1.77 (1.11-2.08)	**0.016**
Destination therapy	0.712	2.04 (1.14-3.64)	**0.016**
Surgery combined with LVAD	0.915	2.49 (1.26-4.95)	**0.009**

Bold p-value are for significant results (i.e. p<0.05).

μmol/L before LVAD, systemic hypertension at baseline, destination therapy as LVAD indication and any cardiac surgery combined with LVAD (Table 3). Notably, each predictor increases by 2-fold the risk of death. The survival depending on the number of predictors per patient is represented in Figure 3 and shows a gradual increase in the risk of death with increasing number of predictors. Interestingly, patients with abnormal BMI and 0 or 1 predictor exhibited the same 36-month survival than those with normal BMI. However, LVAD recipients with 2 or 3 predictors experienced lower but similar survival. Last those with 4 predictors had the worst outcomes. To summarize, patients with abnormal BMI can be divided in 3 groups of risk depending on the number of predictor factors per patient: i.e., 0 to 1 predictor = low risk of 1-year mortality (29% and 31%, respectively), 2 to 3 predictors = intermediate risk of 1-year mortality (51% and 52%, respectively), and 4 predictors = high risk of 1-year mortality (83%).

Discussion

The major findings of this multicenter study are (1) more than half of the LVAD candidates have an abnormal BMI; (2) LVAD recipients with abnormal BMI have poor outcomes, especially those with low BMI; (3) total bilirubin before LVAD, hypertension, destination therapy, and any cardiac surgery combined with LVAD are the 4 predictors of mortality among LVAD candidates with abnormal BMI;



Number at risk							
Normal BMI	279	186	120	83	64	51	40
Abnormal BMI + 0-1 predictor	221	146	95	69	50	27	19
Abnormal BMI + 2 predictors	97	45	33	25	22	14	9
Abnormal BMI + 3 predictors	49	24	18	17	15	13	9
Abnormal BMI + 4 predictors	6	1	1	0	0	0	0

Figure 3. Survival curves depending on the number of predictors per patient among the LVAD population with abnormal BMI.

and (4) there was a gradually increased risk of mortality depending on the number of predictors per patient.

It has been well established that overweight and obesity are associated with an increased risk of HF.[15] Additionally, in patients with end-stage HF, the incidence of obesity may range from 25% to 36% that considerably reduces the probability of heart transplantation[16,17] and leads to a higher post-transplant morbidity/mortality.[18] Similarly, underweight BMI (<18.5 kg/m^2) can limit access to cardiac transplantation due to a lower probability of donor-recipient size matching. Additionally, an analysis from the International Society for Heart and Lung Transplantation registry observed that an underweight BMI leads to an increased risk of postoperative mortality and serious adverse events after heart transplantation.[19] These results suggest that in patients with end-stage HF and abnormal BMI, LVAD implantation could be an attractive alternative option, especially since the smaller size of new generation devices allows their use in a larger population. In our study, we showed that more than half of the LVAD recipients had an abnormal BMI at the time of pump implantation. Interestingly, this population had a 2-fold longer HF duration before LVAD implantation and more likely received optimal HF drugs. These differences may suggest the challenging management of these patients in France, with a preference for longer drug strategy and a potential reluctance for an early LVAD implantation compared with patients with normal BMI.

Our findings show that patients with abnormal BMI experience lower survival than those with normal BMI and especially those with underweight BMI. Discrepant results have been published thus far and previous works did not show that obesity decreased survival among LVAD recipients.[5−9] However, a recent meta-analysis suggested that obese patients have similar long-term survival after LVAD implantation when compared with nonobese patients.[20] In our study, we showed that patients with high BMI have advanced cardiomyopathy, more dilated left ventricle with more co-morbidities and may potentially explain the higher mortality in this population. Additionally, we observed that these patients more likely experienced a pump replacement and had numerically more pump thrombosis and stroke events, possibly leading to increased mortality. These findings are supported by several studies demonstrating that obesity was associated with an increased risk of LVAD complications.[8,9] However, as previously described, we did not show a relationship between obesity and LVAD-related infections.[21]

Our study also highlights that patients with underweight BMI have worse outcomes. Conversely, a Japanese study has reported excellent outcomes in patients with a small body surface area and receiving an LVAD, probably due to the different patient populations and their extensive experience with these smaller patients.[22] However, previous work showed that patients with small body size had higher post-operative mortality and lower long-term survival.[11] Indeed, despite the development of smaller devices, a minimal body surface area is still required by manufacturers to avoid misalignment of the inflow connector or mechanical compression of cardiovascular structures.[23] This mismatch between BMI and LVAD size could possibly explain the worst outcomes. It is also plausible that underweight patients may have the unnecessary metabolic reserves to overcome the further increased catabolic stress resulting from a stressful surgery and long-term life with LVAD.[24]

In this study, 4 predictors of mortality in LVAD recipients with abnormal BMI were defined. We found that systemic hypertension at baseline was a predictor of death. Indeed, hypertension may impact outcomes in patients with LVAD by decreasing pump flow, increasing LV filling pressure leading to worsening heart failure symptoms and promoting de-novo aortic insufficiency.[25] Additionally, we observed that a high total bilirubin level (i.e., $\geq$16 μmol/L) independently impacts long-term survival. This parameter is known to be a marker of chronic congestion due to right ventricular dysfunction before LVAD implantation and indicates a more severe end-stage HF with multiple organ failure.[26] We also shown that any cardiac surgery combined with LVAD predicted higher mortality in patients with abnormal BMI, which is concordant with previous data showing that this parameter was an independent predictor of postoperative mortality.[27] Indeed, LVAD candidates requiring a combined surgery usually require a longer and more complex surgery possibly leading to myocardial injuries. Last, we found that destination therapy indication was associated with a higher risk of death, since these patients are not candidates for heart transplantation. Importantly, we highlighted that the number of predictors per patient strongly impacts survival. Indeed, patients with abnormal BMI and 0 or 1 predictor are at low risk of death, those with 2 or 3 predictors have an intermediate risk of death and patients with 4 predictors may be defined at a high risk of death. Nevertheless, a small panel of abnormal BMI patients was classified in this group and this result should be interpreted cautiously.

Our observational study has some limitations, including its retrospective design that may have affected the results. Additionally, we cannot provide an extensive description of the nutritional status (i.e., albumin or prealbumin parameters) among obese or underweight patients. Furthermore, it has been established that LVAD implantation is associated with long-term improvement in nutrition.[28] Unfortunately, we did not collect the evolution of the BMI after LVAD implantation and consequently, we cannot investigate the impact of the BMI normalization on outcomes in LVAD patients. Also, we acknowledge that these findings reflect clinical practice in France but may not necessarily be extended to other populations. Last, we did not evaluate the impact of BMI in patients scheduled for HeartMate 3. Further studies are warranted to assess the outcomes of abnormal BMI in this population.

In conclusion, LVAD candidate with overweight/underweight BMI is extremely common in clinical practice. Importantly, LVAD recipients with abnormal BMI experience lower survival, especially those with underweight BMI. Four predictors of mortality have been identified for the LVAD population with abnormal BMI, differentiating those a low, intermediate and high risk of death.

Disclosures

The authors have no conflicts of interest to disclose.

Credit Authors Statement

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