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Incidence and Predictor Variables of Pressure Injuries in Patients Undergoing Ventricular Assist Device and Total Artificial Heart Surgeries: A Systematic Review.

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Incidence and Predictor Variables of Pressure Injuries in Patients Undergoing Ventricular Assist Device and Total Artificial Heart Surgeries: A Systematic Review.

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ABSTRACT

BACKGROUND

Cardiac surgery patients have some of the highest reported incidence and prevalence of pressure injuries (PI). A growing subset of cardiac surgery include patients with end-stage heart failure who undergo ventricular assist device (VAD) or total artificial heart (TAH) surgery. The risk of PI and their natural history of development in this population are unknown.

OBJECTIVES

To perform a systematic review of the literature to identify the prevalence, incidence, and risk factors of PI development in patients undergoing VAD-TAH surgery.

METHODS

The preferred reporting items for systematic reviews and meta-analyses or PRISMA statement guided this systematic review. Quality of evidence was determined using the Johns Hopkins Nursing Evidence-Based Practice Rating Scale. Two reviewers independently appraised manuscripts matching the eligibility criteria for study inclusion. Four databases including PubMed, CINAHL, Web of Science, Google Scholar, and hand searches of journals based on reference lists from included studies were utilized. Initial results of this primary search revealed zero studies that met inclusion and this search methodology was confirmed by medical librarian consultation. A secondary search dropping keywords of VAD-TAH and instead focusing on studies of *on-pump* cardiac surgery and mixed surgical studies where cardiac surgery patients were included was conducted.

RESULTS

312 articles were identified from the databases with eight additional articles from hand searches. Following abstract review, 208 were excluded for not meeting inclusion criteria or study quality metrics. 77 articles were read in full, with 61 excluded, leaving 16 articles for inclusion. 31 risk factors were identified for PI development in *on-pump* cardiac surgery patients with 11 risk factors being most commonly identified as significant in multivariate analysis across all studies.

CONCLUSIONS

The prevalence, incidence and natural history of PI in VAD-TAH patients remains unknown. This population may be at higher risk of PI development due to: greater severity of illness preoperatively, longer operating room times, longer cardiopulmonary bypass time, and associated comorbidities, among others. The results of risk factors associated with *on-pump* cardiac surgery patients will guide a subsequent 8-year retrospective study of the PI risk factors that potentially confront VAD-TAH patients, to gain more insight into PI development in this subset of the cardiac surgery population.

INTRODUCTION

Pressure ulcers are defined as, "localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear" [1]. In 2016, the term pressure ulcer was revised to pressure injury by the National Pressure Ulcer Advisory Panel (NPUAP) and this term was defined as, "localized damage to the skin and underlying soft tissue usually over a bony prominence or related to a medical or other device. The injury occurs because of intense and/or prolonged pressure or pressure in combination with shear. The tolerance of soft tissue for pressure and shear may also be affected by microclimate, nutrition, perfusion, comorbid conditions and condition of the soft tissue"[2]. The revisions were made to attempt to more adequately reflect PI staging, particularly of Stage 1 and Deep Tissue Pressure Injury, as these pressure and shear related injuries do not always ulcerate.

Globally, PI prevalence ranges from 27.3% to 72.5%. [1,3]. In acute care settings, prevalence ranges from 0-49% contingent on the care setting and patient population. Over 2.5 million patients develop PI and cause 60,000 deaths in the United States per year [4]. In the U.S., PI treatment costs may exceed $26.8 billion dollars annually [5], increase length of stay (LOS) by 11 days, and adds $30,000 to overall costs per admission. [6–9] Over 100 risk factors have been associated with the development of PI. Historically, cardiac surgery patients have been described as at high risk for PI development with incidence rates between 7-29.5% [10–17]. Risk factors for identification of PI in cardiac surgery patients remains a needed and clinically relevant area of research given the high incidence, cost, associated patient burden and lack of advancement in prevention of PI in cardiac surgery patients [18,19].

Heart Failure and VAD-TAH Surgeries

A growing subset of the cardiac surgery patient population includes those with advancing heart failure (HF) who require implantable ventricular assist devices or a total artificial heart (VAD-TAH). In the U.S., the number of persons with HF is anticipated to exceed eight million people by 2030 and is projected to be the leading cause of disability [20]. One retrospective study in patients hospitalized with systolic HF investigated LOS, in-hospital mortality and associated predictors. Data were extrapolated from three payer based research databases [21]. Of the 17,517 patients identified in the study, PI were present in 4% of subjects with associated increased LOS by 1.36 days ($p<0.0001$) due to PI in every payer category (commercial 158/4109; Medicaid 76/2118; Medicare 446/11,370), evidencing a significant patient and economic burden. The use of VAD-TAH devices is becoming the standard of care for both bridge-to-transplant and long-term destination therapy in end stage HF. Between 2009 and 2014, the percentage of heart transplant recipients who had a VAD at the time of transplant increased from 33.6% (n=631) to 44.9% (n=1018) [22]. In an interrupted time series intervention study of 341 patients in two cardiac surgery intensive care units, the only statistically significant variable for PI development was heart failure ($p=0.002$) [15]. Due to the high rate of PI in the cardiac surgery population, the impact of VAD-TAH surgery on PI development warrants investigation.

Patients undergoing VAD-TAH procedures may be at greater risk for PI development compared to patients requiring a Coronary Artery Bypass Graft (CABG) procedure related to: 1) nature and length of the VAD-TAH procedure including cardiopulmonary bypass, 2) length of stay (LOS), and 3) physiological vulnerability and comorbidities of patients with advanced HF. The VAD-TAH procedure has greater surgical times than CABG (3-6 hours for CABG vs. 6-9 hours VAD-TAH), plus higher total immobility, defined henceforth as the total time from preoperative admission in the perioperative suite to first turn in the intensive care unit post

operatively. Average LOS for CABG surgery is five days, while VAD and TAH average LOS is 20 and 18 days, respectively (Cotts et al., 2014; [24]. Finally, patients who need VAD-TAH have advanced heart failure with severely reduced cardiac function, whereas patients who undergo CABG have coronary artery occlusion with or without existing heart failure. This differentiation is significant. Patients with advanced left ventricular failure or biventricular failure requiring VAD-TAH have higher preoperative American Society of Anesthesia (ASA) scale scores compared to patients having CABG. ASA scale scores range from I (mild systemic disease) to V (moribund patient not expected to survive without surgical intervention [25]. ASA scores greater than or equal to three are associated with higher operating room PI rates [26]. Fred and colleagues (2012) reported that for each one-point increase in ASA, the odds of developing PI increased by 149% in a sample of 138 surgical patient from mixed specialties in a retrospective review.

CARDIOPULMONARY BYPASS

Cardiopulmonary bypass (CPB) creates a non-pulsatile, bloodless surgical field while reintroducing oxygenated blood back into the systemic circulation [27]. Use of CPB is associated with multisystem organ dysfunction including cardiac, pulmonary, renal, hepatic, gastric and cerebral failure. The severity and extent of organ failure depends on the duration of: CPB, surgery, aortic cross clamping and plasma lactate levels [28]. A systematic review of 23 studies with a total sample size of 7,976 patients identified that on-pump cardiac surgery patients had significantly higher incidence of stroke, renal failure, ventilation time and sternal infection [29]. Systemic inflammation and subsequent organ and tissue damage is further complicated by the non-pulsatile nature of blood flow associated with CPB. Systemic changes associated with CPB include a severe systemic inflammatory response syndrome caused by activation of both cellular and solid proteins [27] as described in TABLE 1. Alterations to vascular permeability and tissue edema is most

profound in patients undergoing CPB for 80 minutes or longer [30]. Despite the focus of much research on injury to body organs from CBP, the effect of CPB on the skin has not been reported.

Given the high prevalence of PI associated with CABG procedure and the additional vulnerability associated with advanced HF and VAD-TAH surgical procedures, it is hypothesized that the VAD-TAH surgery represents the highest level of risk for PI development among cardiac surgery patients. However, the actual incidence is unknown and represents a large gap in our current understanding of PI etiology in this population.

Therefore, the aim of this systematic review of the literature is to describe the prevalence, incidence and risk factors associated with PI development in heart failure patients undergoing ventricular assist device or total artificial heart (VAD-TAH) surgery.

METHODS

The design for systematic review of the literature utilized the methods described in the preferred reporting items for systematic reviews or PRISMA statement [35]. Strength and quality of evidence was determined using the Johns Hopkins Nursing Evidence-Based Practice Rating Scale seen in Figure 1 [36]. Risk of bias associated with the identified studies was determined using the Cochrane tool for assessing risk of bias [37].

Inclusion criteria for the systematic review involved studies reporting the development of PIs in cardiac surgery patients undergoing VAD or TAH surgery. Specifically, retrospective or prospective observational studies reporting study incidence or prevalence of pressure injuries within the perioperative, intraoperative or immediate postoperative period were considered. Study characteristics including English only language and a timeframe of 1966-2017 to coincide with the

first reported implantation of a mechanical support device for myocardial recovery after heart surgery [38].

Informational sources utilized for study identification and inclusion included PubMed, CINAHL, Web of Science, Google Scholar, and hand searches of journals based on reference lists from included studies. Two search strings of keywords utilized for PubMed and CINAHL databases including associated filters are show in Figure 2. For these initial searches, 240 articles were found, 30 were selected after abstract review, however after full text review, 0 articles were identified that included VAD or TAH patients which reported on PI risk factors, incidence, prevalence or natural history within these patients. The results were validated by the inclusion of a medical librarian who confirmed via independent search the inability to identify any articles matching the eligibility criteria for this systematic review.

Secondary Review

Therefore, a secondary search was conducted *removing* keywords specific to ventricular assist device and total artificial heart and focusing on *on-pump* cardiac surgical procedures. The same databases were utilized. The search included a revision to the eligibility criteria which included only studies from 2007 to the present. This decision follows the changes to the National Pressure Ulcer Advisory Panel's updated pressure ulcer staging system [39] which included the addition of suspected deep tissue injury and unstageable pressure ulcer classifications. Further, the time frame is justified as the morbidity of cardiac surgical patients is considerably different in the last 10 years than during the historical period between 1966-2007. Further inclusion criteria allowed, 1) all retrospective or prospective studies including patients undergoing on-pump (e.g. use of cardiopulmonary bypass during cardiac surgery) cardiac surgery procedures or 2) reported systematic reviews and meta-analyses of cardiac surgery patients and 3) studies of intraoperative

PI risk where cardiovascular surgery patients were part of the sample. Grey literature was evaluated and included if such sources described research studies with sufficient methodological description to determine strength of evidence and quality. Articles that were strength of evidence lower than III and/or quality scores of C or less were excluded. Similarly, articles were not included if designated as off-pump cardiac surgery or vascular/thoracic procedures. Duplicates and reprinted publications were removed to reduce the risk of transverse and longitudinal bias. A flow diagram of study records identified can be found in Figure 3. Search data and identified study records were managed with Excel spreadsheet software in chronological order with the authors (TB & JB) reviewing each full text article independently for inclusion, strength of evidence and quality, as well as risk of bias. Following review, these records were extrapolated to the evidence table shown in Table 1.

On-pump cardiac surgery with CPB cannot be compared to other non-cardiac surgeries due to the differences in perioperative, operative and postoperative patient characteristics [32]. Therefore, articles including off-pump cardiac surgery, or beating heart surgery, were removed secondary to the CPB research indicating that off-pump patients are at considerably less risk for complications including multisystem organ failure [33]. Since off-pump surgical technique was developed in the mid-1990s, it was assumed any articles that did not differentiate on-versus-off pump CABG were on-pump, given reports that the use of off-pump technique was negligible in 1995, about 10% in 1999 and estimated to be around 50% by 2005 [40].

RESULTS

ON-PUMP CARDIAC SURGERY STUDIES

Based on the outcomes of the VAD-TAH review as described above, the secondary aim of this systematic review was to identify articles involving on-pump cardiac surgery patients that represent the closest surrogate for the VAD-TAH population. In total, 312 articles were identified from the respective databases with eight additional articles identified by hand searches. Following abstract review, 208 were excluded for not meeting the appropriate surgical type, procedure, date range or study quality metrics. Seventy-seven articles were reviewed, with 60 excluded secondary to: reprints, non-English language, being off-pump populations, vascular or thoracic procedures and poor strength of evidence and quality scores. An evidence table of all 17 included articles is provided in TABLE 2. Seven articles included studies involving cardiac surgery patients only, whereas nine included mixed surgical populations in addition to ICU and operating room locations. Common risk factors found between the respective studies who performed multivariate analysis are found in TABLE 3.

Cardiac Surgery Population

Feuchtinger and colleagues (2007) identified that 33/53 consecutively enrolled CABG patients developed 47% of ulcers on post-operative day 0 and 15% of the remaining pressure injuries between day 1 and day 7 after surgery. The primary limitation of this study was the high rate of attrition as patients were dropped from the study after they left the ICU. The primary purpose of this study was to compare post-operative risk assessment scores or predict PI development using the Norton, Water low and Braden Risk Assessment Tools. The Braden score was found to be most appropriate for the CABG population given its superior sensitivity (78%) and specificity (29%) at a cut-off point of 16. Remaining scores indicated that patients should all be considered as at risk for the first five postoperative days.

A unique consideration after CABG surgery includes the impact of mental health on the post-operative complications. In a study of 135,701 CABG surgeries in the New York state database, patients with mental disorders (schizophrenia, major depression, dementia, bipolar disorder, and other psychiatric conditions) were found to have higher rates of PI than those without mental disorders (7.3/1000 vs. 1.8/1000; AOR 1.42, p=.006) (Li, Glance, Cai, & Mikael, 2008). Additionally, the effect of mental health disorders on patient safety varied widely between hospitals suggesting different facilities are not as adept as others to care for patients with mental disorders. In this study, the adjusted odds ratio (OR 1.32; p<0.01) suggest that having a psychiatric disorder alone increases the risk of complication following CABG.

In a prospective longitudinal study of 100 cardiac surgery patients in Spain, 18% of patients developed PI, yet no statistically significant variables were found to differentiate the PI and non-PI groups.[42] No relationship between the duration of surgery, cardiopulmonary bypass time, blood pressure or hypothermia and development of a PI was reported by the researchers.

A descriptive cross-sectional study of 333 patients in Iran [43] identified a 21.3% (n=71) PI incidence rate. Of these, 94% were identified immediately after the procedure, within the first 24 hours in ICU or after transferring to the general floor. Risk factors associated with PI development in multivariate analysis included age, gender, hypertension, myocardial infarction, intraoperative hypoxemia, not having a specialty mattress post operatively, blood pressure sustained less than 80mmHg systolic, requiring reoperation, low hematocrit, low albumin and increased length of hospital stay leading to increased PI risk.

In a study of 286 adult and pediatric cardiac surgery patients from China, the PI incidence rate in adults was 18.8%, with significant predictors of corticosteroid administration (p<0.05) and length of surgery (p=0.03)[44]. The authors' stated that cardiopulmonary bypass, gender, weight,

intraoperative and post-operative vasoactive medications were not significant predictors of PI risk. In a separate prospective consecutive cohort study of 149 patients in a cardiac ICU in China [45], a 24.8% incidence rate of PI development was reported with 94.6% of identified as stage 1 and the remainder (5.4%) stage 2. Logistic regression indicated that valvular disease (OR 6.43, 95% CI 1.44, 28.69; p=0.063) coronary artery disease (OR 8.8, 95% CI 1.74, 44.62; p<0.03), weight (OR 0.971, 95%CI 0.94-1.004; p<0.084) and surgery duration (OR 1.005, 95%CI 1.000-1.010; p<0.036) were the major risk factors for ulceration. A primary limitation of this study was the author's use of the 2007 National Pressure Ulcer Advisory Panel (NPUAP) pressure ulcer staging definitions, yet inclusion of only Stages 1-4 PI as their method of classification. Therefore, it is possible that the high rate of reported stage 1 pressure injuries reflects the misclassification of deep tissue pressure injuries (DTPI).

Robich and colleagues investigated rates and risks associated with "never events" using the National Inpatient Database (NIS) between 2003 and 2011 for all patients undergoing adult cardiac operations, specifically looking at CABG, valve surgeries, and thoracic aneurysm repair [46]. The study included 588,417 patients among whom 4377 "never events" were reported. PI rates were reported as 4% over the entire study period, however, this number likely reflects historical bias as rates were reported as 0% between 2003-2007 and 12% between 2008-2011. The Centers for Medicare and Medicaid Services (CMS) decision to no longer reimburse hospitals for hospital acquired conditions such as PIs at a higher diagnostic category on October 1, 2008, likely resulted in the high rate of change between these two-time periods. However, the study did determine that cardiac surgery patients who experience a never event were at an increased risk of morality (OR 2.63, 95% CI 2.16-3.2, p<0.001), length of stay (MR 2.03, 95%CI 1.98-2.09, p<0.001) and total hospital charges (MR 1.73, 95% CI 1.68-1.78; p<0.001).

Mixed Surgical Population

Mixed surgical patient studies were considered to identify other potential risk factors but adds selection bias due to variance in underlying comorbid states, operative body position and the lack of CPB for non-cardiac patients. Liu and associates (2012) performed a meta-analysis of six studies (4 cardiac surgery, 2 mixed surgical populations) of 2453 to investigate the effect of diabetes mellitus (DM) on the development of PIs during surgical procedures. The incidence rate across studies was 11.8%, with no significant heterogeneity (X^2_5 =1.98, p=0.85, I^2=0%) between the studies. All studies were listed as IIB evidence and 7/8 for quality according to the Newcastle-Ottawa scale. The meta-analysis revealed that DM was significantly associated with the development of PI (OR 2.15 (95%CI: 1.62-2.84; Z-5.32, p<0.00001, fixed effects model OR=2.13). Even after the removal of one retrospective study, the odds ratio was still significant (OR=2.03) [47]. These findings were supported by a second meta-analysis of 13 studies including total comparison groups of patients with PI (n=2367) and patients without (n=12053) showing DM to be a significant risk factor across surgical types with a pooled odds ratio of 1.74 (95%CI= 1.40-2.15, I^2=51.1%) [48]. When isolating the four studies involving cardiac surgery patients alone, DM remained a significant risk factor (OR=2.0, 95%CI=1.42-2.82, I^2= 0%). Importantly the authors identified an additional consideration in the cardiac surgery population to be limited movement associated with IABP and VAD devices, however these interventions modalities were not evaluated in the statistical model.

A systematic review of the literature by Rao and colleagues (2016) reviewed 12 studies looking at critical care, surgical ICU or cardiac surgery ICU for preoperative risks of PI development. The authors described significant risk factors according to preoperative, intraoperative and postoperative findings. The highest odds for PI development included spinal

cord injury (OR 16.8), history of previous PI (OR 13.51), and hemodialysis within 24 and 48 hours of surgery (OR= 4.77; 9.43 respectively), DM (OR=2.70), fecal incontinence (OR 3.27) limited mobility (4.42), and mechanical ventilation (OR=4.82) The researchers highlighted the relative absence of DTPI in the studies in this review and suggested that "hypoxic reperfusion" is linked to DTPI and has not been sufficiently included in previous frameworks of PI development. Articles addressing DTPI include a 5 year retrospective study of 119 patients in a seven surgical ICUs [49]. The authors found that for every hour the patient spent in surgery, the risk of DTPI increased by 20%. Other significant variables included dialysis (OR 4.0, 95%CI 06-0.99, p=0.05), cardiogenic/septic shock (OR=10, 95%CI 0.025-0.43, p=0.002), low diastolic blood pressure (OR 0.93, 95%CI 0.88-0.99, p=0.02) and time of surgery in hours (OR 1.20, 95% 1.07-1.33, p=0.001). Cox and Roche (2015) identified an incidence of 13% (41/306) in a retrospective correlational study of 306 patients in a medical surgical and cardiac surgical ICU [50]. Of these pressure injuries, 39% were DTPI and 56% were found on the sacrum. The authors identified significant risk factors for PI development included longer infusion times of: vasopressin (32 hours vs 87 hours, p=0.005), high dose vasopressin (20 hours vs. 57 hours, p=0.03) and patients receiving both vasopressin and norepinephrine (X^2=39.3, p<0.001). Vasopressin was the only vasoactive medication to emerge as a significant predictor in multivariate analysis. The authors commented that the dose of 0.03 U/min at longer infusion times may be a tipping point for pressure injury development.

A retrospective matched case-control study of 32,963 patients from a level-one trauma center in the US investigated the time in the operating room as a risk factor for PI.[51] In this study there was an overall 2.8% incidence rate and time in surgery was identified as a significant risk with increasing odds over time (<2 hours OR=1.1; 2-4 hours OR=1.2; 4-6 hours OR= 1.6; >6 hours OR 6.4). Additionally, documentation of PI occurrence 72 hours after surgery was found in 78%

of patients, with only 4.5% present within the first 24 hours, suggesting an extended assessment period after surgery is necessary for PI identification [52]. A prospective convenience sample of 258 patients undergoing operations of 3 hours or more (21/258 cardiac; 69/258 general surgery) found a PI incidence rate of 8.1% overall [53]. Significant risk factors identified in logistic regression included use of specific Operating Room table pads: foam pad (OR=14.740), OR table with Foam pad and valve (OR=3.397), use of gel pad on the OR table (OR=2.809), use of the Jackson table (OR 2.231) and preoperative patient temperature (OR 1.014). Of those patients who developed PI, 33.7% of the PI group had ASA scores of 2, while 53.5% had ASA scores of 3. The use of ASA scores to identify risk is further supported by a retrospective secondary analysis of 2695 patients from cardiovascular, burn and surgical ICUs reported a 10% PI incidence rate and identified ASA score of 4 or 5 [26] as a significant predictor of PI development. Propensity matching of 122 cases identified a significant intraoperative risk factor to be receipt of blood products (OR 1.71, 95%CI, 1.03-2.84, p=0.04).

DISCUSSION

The cardiac surgery population has historically been identified with intraoperative PI incidence rates as high as 29.5%, [11,54]. Subsequent prospective cohort studies of subpopulations such as cardiac surgery bypass grafting (CABG), the most commonly studied cardiac surgical intervention, have shown incidence rates as high as 53.4% in the cardiac ICU [55] yet the actual incidence and prevalence is still unknown. One of the greatest limitations of available literature reviews and research in the cardiac surgery population is the preponderance of these earlier studies occurring prior to the description and recognition of deep tissue pressure injuries (DTPI) (Black, Brindle, & Honaker, 2016). Review of articles prior to inclusion of DTPI in National Pressure Ulcer Advisory Panel Guidelines in 2007 [39] would lead to historical bias. For example, three studies commented

on “violet pressure ulcer” (Feuchtinger et al., 2005), ecchymosis as a risk factor for PI [14] and in Schoonhoven and colleagues’ study, 34 patients were excluded due to symptoms that were not common to known PI staging classifications systems at the time [16]. The authors described, “painful or numb discoloration that disappeared (partially) when light pressure was applied; sharply defined; indurated; lasting 13-21 days despite relief of pressure, and/or bright red discoloration.” (p.169). These inconsistencies in assessment likely led to misclassification of many post-operative PI prior to 2007 given the high rate of reported stage 1 and stage 2 PI in these early studies.

Additionally, an important consideration that is not addressed in the studies regarding PI etiology to date is the distinction between pulsatile versus non-pulsatile blood flow both during CPB intraoperatively and during the use of VAD devices in the postoperative period. Intraoperatively, non-pulsatile blood flow, theoretically, may not provide sufficient intravascular pressure to open the dermal capillary sphincters, possibly impacting cutaneous vascularization. Moreover, during CPB, the impact of volumetric dilution of the circulating serum on perfusion of the cutaneous complex is not well understood. Contrasting the concern over pulseless blood flow during CPB, is the understanding that patients with VAD devices who are ambulatory after surgery, do not have spontaneous cutaneous vascular collapse despite being on an ongoing pulseless flow device.

Animal research investigating the concerns over end organ perfusion between pulsatile and non-pulsatile circulation has been described. A porcine study of 20 pigs randomized to 4 groups (pulseless and pulsatile groups at two different pressure settings evaluated within the renal artery) were evaluated for impact of perfusion on renal recovery following normothermic ischemia [57]. In the high pressure pulseless and pulsatile groups (renal artery pressure 65 ± 1.6 mmHg) no differences were seen in renal recovery. However, in the lower pressure groups (40 ± 1.1 mmHg)

there was a significant difference in recovery of renal blood flow, ATP recovery and VO2, with pulsatile perfusion being superior to pulseless perfusion in all outcomes. Further, results indicated no difference in renal histology between the pulseless or pulsatile groups. A later study reported the impact of end-organ function during chronic non-pulsatile circulation using an animal model of 15 sheep allocated to LVAD or control group which were sacrificed electively at 30, 90, 180 and 340 days for evaluation [58]. The researchers report that there were no histologic differences between organs of pulsatile and non-pulsatile animals, no significant difference in mean blood pressure, however significantly elevated plasma renin levels in pulseless animals was found. Feng and colleagues evaluated the short-term effects of completely non-pulsatile versus pulsatile circulation on peripheral vascular permeability of 10 calves with continuous flow Heartmate III rotary pumps [59]. Five calves had their pump speeds modulated to result in a low frequency pulse pressure of 10-25mmhg (physiologic range) at 40 pulses a minute, while the remaining five had non-pulsatile systemic circulation. Researchers assessed skeletal muscle biopsies at postoperative days 1, 7 and 14 with additional comparisons of tissue water content, morphologic alterations and comparisons of immunohistochemistry in respective biopsies. Results indicated no significant differences in tissue water content, or skeletal muscle morphology at any postoperative time point. There were no significant differences in the expression or distribution of study immunohistochemical biomarkers between the groups causing researchers to observe no peripheral endothelial injury or peripheral microvascular permeability in either group. These animal studies, therefore, raise the question as to whether pulseless blood flow alone is a risk factor for PI development or is systemic inflammatory response associated with total CBP time more associated with downstream impact to end tissue perfusion?

LIMITATIONS

First, as there were no articles identified in the literature for VAD-TAH surgery patients and PI, there is inherent risk of selection bias in the creation of the secondary search string as the author attempted to select a surgical population that approximated the risks associated with VAD-TAH procedures, namely, on-pump cardiac surgery.

There is considerable probability that many Stage 1 PI and stage 2 PI reported in these studies were actually deep tissue injury, which greatly changes the severity of the injury itself. This fact was highlighted in the study by Cox and Roche (2015) as their results contrasted historical outcomes with 39% of the observed pressure injuries being DTPI with 56% of them found on the sacrum. Another possible explanation for this difference in reported severity may be the overall morbidity of patients and advanced, life-prolonging intensive care management in 2017 versus the studies of the early 1990s.

CONCLUSION

The incidence and natural history of PI development in the VAD and TAH cardiac surgery patient remains unknown. This finding represents a significant gap in our understanding of pressure injury etiology and prevention warranting on-going research. Additionally, a systematic review of 1533 articles failed to identify studies specifically investigating interventions for PI prevention in the cardiac surgery population [60]. This gap in existing evidence does little to reduce the risk and rate of PI in cardiac surgery patients [54] and highlights the critical need to identify risk factors leading to PI development to guide prevention in the cardiac surgery population. The systematic review reported here will guide the first, 8-year retrospective analysis of VAD and TAH patients to identify incidence, and predictors of PI development in a large academic university health center in the United States.

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FIGURE 1. John's Hopkins Nursing Evidence-based Practice Rating Scale

JHNEBP EVIDENCE RATING SCALES

STRENGTH of the Evidence	
Level I	Experimental study/randomized controlled trial (RCT) or meta analysis of RCT
Level II	Quasi-experimental study
Level III	Non-experimental study, qualitative study, or meta-synthesis.
Level IV	Opinion of nationally recognized experts based on research evidence or expert consensus panel (systematic review, clinical practice guidelines)
Level V	Opinion of individual expert based on non-research evidence. (Includes case studies; literature review; organizational experience e.g., quality improvement and financial data; clinical expertise, or personal experience)

QUALITY of the Evidence		
A High	Research	consistent results with sufficient sample size, adequate control, and definitive conclusions; consistent recommendations based on extensive literature review that includes thoughtful reference to scientific evidence.
	Summative reviews	well-defined, reproducible search strategies; consistent results with sufficient numbers of well defined studies; criteria-based evaluation of overall scientific strength and quality of included studies; definitive conclusions.
	Organizational	well-defined methods using a rigorous approach; consistent results with sufficient sample size; use of reliable **and** valid measures
	Expert Opinion	expertise is clearly evident
B Good	Research	reasonably consistent results, sufficient sample size, some control, with fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence
	Summative reviews	reasonably thorough and appropriate search; reasonably consistent results with sufficient numbers of well defined studies; evaluation of strengths and limitations of included studies; fairly definitive conclusions.
	Organizational	Well-defined methods; reasonably consistent results with sufficient numbers; use of **reliable and valid** measures; reasonably consistent recommendations
	Expert Opinion	expertise appears to be credible.
C Low quality or major flaws	Research	little evidence with inconsistent results, insufficient sample size, conclusions cannot be drawn
	Summative reviews	undefined, poorly defined, or limited search strategies; insufficient evidence with inconsistent results; conclusions cannot be drawn
	Organizational	Undefined, **or** poorly defined methods; insufficient sample size; inconsistent results; undefined, poorly defined or measures that lack adequate reliability or validity
	Expert Opinion	expertise is not discernable or is dubious.

**A study rated an A would be of high quality, whereas, a study rated a C would have major flaws that raise serious questions about the believability of the findings and should be automatically eliminated from consideration.*

Newhouse R, Dearholt S, Poe S, Pugh LC, White K. The Johns Hopkins Nursing Evidence-based Practice Rating Scale. 2005. Baltimore, MD, The Johns Hopkins Hospital; Johns Hopkins University School of Nursing.

FIGURE 2. Search Strategy for Systematic Review of VAD-TAH Patients

VAD-TAH String 1

(((((("Heart Failure"[Mesh] OR Heart Failure[TIAB]))) OR (("Cardiovascular Surgical Procedures"[Mesh] OR Cardiovascular Surgical Procedure*[TIAB]))) OR (((((("Vascular Assist Device*[TIAB] OR Artificial Ventricle*[TIAB] OR Heart Assist Pump*[TIAB] OR Heart Assist Device*[TIAB] OR Ventricular Assist Device*[TIAB] OR Artificial Heart Ventricle*[TIAB] OR Artificial Heart*[TIAB]))) OR (((((("Heart, Artificial"[Mesh]) OR Artificial Heart[TIAB]))) OR ((Implantable Device*[TIAB]) AND (Heart patient*[TIAB] OR Cardiac Patient*[TIAB])))) OR (("Heart-Assist Devices"[Mesh] OR "Heart, Artificial"[Mesh]))) OR (((Device*[TIAB])) AND ((Heart Lung Bypass*[TIAB] OR Cardiopulmonary Bypass*[TIAB])))) OR "Cardiopulmonary Bypass"[Mesh]))) AND ((("Pressure/adverse effects"[Mesh]) OR Deep Tissue Injur*[TIAB]) OR (("Pressure Ulcer"[Mesh] OR Pressure Ulcer*[TIAB] OR Bedsore*[TIAB] OR Pressure Sore*[TIAB] OR Decubitus Ulcer*[TIAB] OR Bed Sore*[TIAB]))) Filters: English

VAD-TAH String 2

(((((("Heart Failure"[Mesh] OR Heart Failure[TIAB]))) OR (("Cardiovascular Surgical Procedures"[Mesh] OR Cardiovascular Surgical OR “Operating Room” OR “Operating Theatre” OR “Intraoperative” OR Procedure*[TIAB]))) OR (((((("Vascular Assist Device*[TIAB] OR Artificial Ventricle*[TIAB] OR Heart Assist Pump*[TIAB] OR Heart Assist Device*[TIAB] OR Ventricular Assist Device*[TIAB] OR Artificial Heart Ventricle*[TIAB] OR Artificial Heart*[TIAB]))) OR (((((("Heart, Artificial"[Mesh]) OR Artificial Heart[TIAB]))) OR ((Implantable Device*[TIAB]) AND (Heart patient*[TIAB] OR Cardiac Patient*[TIAB])))) OR (("Heart-Assist Devices"[Mesh] OR "Heart, Artificial"[Mesh]))) OR (((Device*[TIAB])) AND ((Heart Lung Bypass*[TIAB] OR Cardiopulmonary Bypass*[TIAB])))) OR "Cardiopulmonary Bypass"[Mesh]))) AND ((("Pressure/adverse effects"[Mesh]) OR Deep Tissue Injur*[TIAB]) OR (("Pressure Ulcer"[Mesh] OR Pressure Ulcer*[TIAB] OR Bedsore*[TIAB] OR Pressure Sore*[TIAB] OR Decubitus Ulcer*[TIAB] OR Bed Sore*[TIAB])))

CARDIAC SURG, NO-DEVICE 1

(((((("Heart Failure"[Mesh] OR Heart Failure[TIAB]))) OR (("Cardiovascular Surgical Procedures"[Mesh] OR Surgery OR Cardiovascular Surgical Procedure*[TIAB]))) AND Intraoperative AND (Heart patient*[TIAB] OR Cardiac Patient*[TIAB])))) OR ((Heart Lung Bypass*[TIAB] OR “on-pump” [TIAB] OR Cardiopulmonary Bypass*[TIAB])))) OR "Cardiopulmonary Bypass"[Mesh]))) AND ((("Pressure/adverse effects"[Mesh]) OR Deep Tissue Injur*[TIAB]) OR (("Pressure Ulcer"[Mesh] OR Pressure Ulcer*[TIAB] OR Bedsore*[TIAB] OR Pressure Sore*[TIAB] OR Decubitus Ulcer*[TIAB] OR Bed Sore*[TIAB]))) Filters: English

FIGURE 3. Flow Diagram of Systematic Review

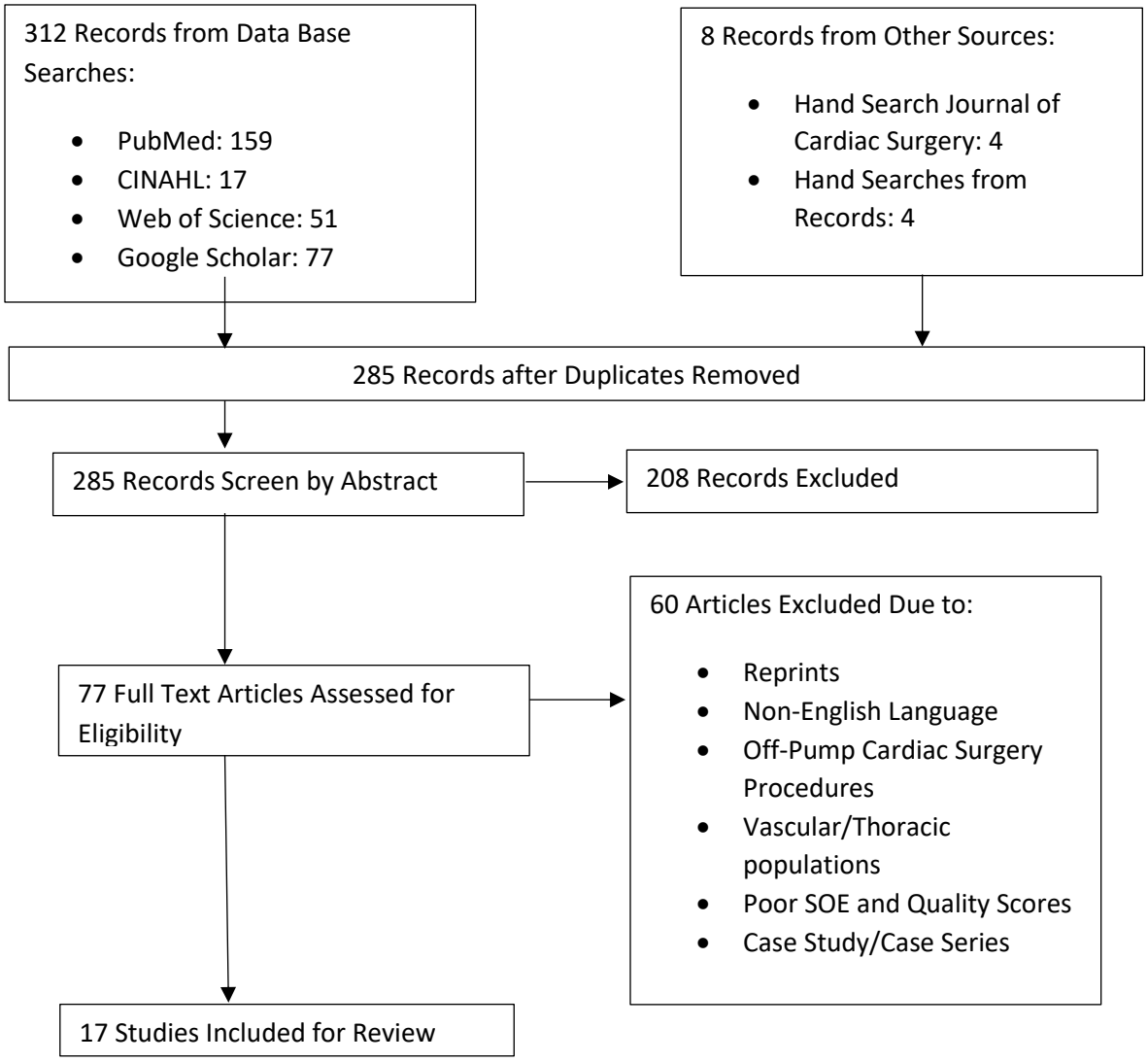

TABLE 1: Cardiopulmonary Bypass Systemic Inflammatory Response

Inflammatory Response Secondary to CPB	**Author**
Activation of complement secondary to contact with CPB circuits and formation of anaphylatoxins and terminal membrane attack complex (C5b-C9).	Esper, et al 2014; Murphy & Angelini, 2004;
Autonomic regulation of peripheral and myocardial arterioles; decreased peripheral vascular resistance on separation from CPB.	Ruel, et al 2004; Song et al, 2017.
Neutrophil activation from anaphylatoxins and kallikreins causing lytic enzyme release and reactive oxygen species.	Ruel, et al 2004; Murphy & Angelini, 2004; Esper et al, 2014;
Cytokine activation increasing inflammation and ROS response and endotoxin production.	Esper, et al 2014;
Metabolic derangement of hyperglycemia, hyperinsulinemia and insulin resistance.	Ruel et al, 2004; Esper, et al 2014;
Profibrinolytic state: elevated tissue plasminogen activator (tPA)	Esper, et al 2014;
Hemodilution leading to decreased oxygen carrying capacity and tissue ischemia.	Wan, et al 2002; Esper et al, 2014;
Ischemia Reperfusion Injury: intracellular calcium trapping, reactive oxygen species and neutrophil-endothelium interactions. Causes access synthesis of superoxides, hydroxyl radicals and peroxynitrate free radicals.	Ruel et al, 2004; Wan et al, 2002;
Embolic events: gaseous, lipoproteins and particulate.	Murphy & Angelini, 2004
Leukocyte Production: causes neutrophil rolling, adherence and transmigration with increased lifespan. Leads to infiltration.	Murphy & Angelini, 2004; Ruel et al, 2004;
Cyclooxygenase and constrictive prostaglandin release	Ruel, et al 2004;

TABLE 2: Evidence Table

Study Author	Design	Strength of Evidence & Quality	Sample/Setting	Study Aim	PI Incidence & Prevalence	Predictors by Multivariate Analysis	Limitations
Feuchtinger, Halfens & Dassen, 2007	Prospective Observational, Convenience Sample	III B	53 Cardiac surgery patients (Germany) ICU Daily Assessment x4 days	To appraise risk assessment using a standardized instrument.	49%- 26/53 on POD 0 2 on POD 1 4 on POD 2 1 on POD 3 0 on POD 4 1 on POD 7 33 or 34 PI in this study… thought 33 from the text.	No multivariate analysis. Sensitivity/Specificity and design of Braden found to best fit CT Surgery population.	Attrition each day (total patients) POD1=53, POD2=36, POD3=20, POD4=17
Li, et al 2008	Retrospective Mental Disorder & Complications after CABG	III A	N=135,701 CABG in NY State Database (US) OR/ICU/Ward	Compare occurrence of postoperative complication in patients with and without	PI w/Mental Disorder 7.3/1000; without 1.8/1000	Decubitus ulcer AOR 1.42 (95%CI 1.10-1.82) p=0.006 Effect of mental disorders on safety	Authors suggest differing ability to care for psychiatric pts was hospital site dependent.

				mental disorders who underwent CABG surgery in NY.		outcomes varied across hospitals (variance of random coefficients 0.16, SE=0.07 for overall complication; 0.79 SE=0.35 for PI. OR 1.32 (p<0.01) for psychiatric disorder alone having increased risk complication.	Mental disorders included: schizophrenia, major depression, bipolar, dementia, and other mental disorders by ICD-9 code.
Ginés, et al 2009	Prospective Longitudinal	III B	100 CT Surg (Spain) OR		18% (18 pts developed 22 PI) 10% had PI Stg 1 on arrival to OR.	No statistically sig variables found between PI and no PI group	No relationship of PI to duration of surgery, cardiopulmonary bypass time, BP or hypothermia.
Primiano, et al, 2011	Prospective observational, convenience sample	III B	258 patients with OR >3 hrs.	Identify prevalence of and risk factors associated with PI formation in	21/258 (8.1%)	Logistic regression: Foam Pad (OR=14.74) Gel Pad (OR=2.809)	ASA 2 (33.7% of PI) ASA 3 ((53.5%)

			Cardiothoracic 21/258 General 69/258	the OR in patients undergoing surgery >3 hr.		Jackson Table (OR=2.231) Preop Temperature (1.014)	No significance: Type anesthesia, surgery, Surgery Length, intraop hypotension/hypoxia, not sig.
Ghavidel et al, 2012	Descriptive Cross-Sectional	III B	333 Patients (Iran) Cardiac Surgery OR and ICU		21.3% (71 PI, 67 in ICU, 4 after transfer ward).	Age, sex, HTN, MI, intraop hypoxemia, mattress, post op inotropes, BP <80mmhg, reoperation, low HCT, LOS, Low Albumin All significant in LR?	Most (what is the n/%) PI found immediately after OR within first 24 hours of ICU.
Liu, He, & Chen, 2012	Meta-analysis	IA	N=2453 (5 US, 1 Belgium) 6 Studies all listed as 2B evidence. 4/6 were cardiac surgery	Aim of meta-analysis was to review evidence related to association between DM and surgery related PI.	11/8% 290/2453 No sig heterogenicity (X^2_5 =1.98, p=0.85, I^2=0%)across studies	DM OR 2.15 (95%CI: 1.62-2.84; Z-5.32, p<0.00001) Fixed effects model DM OR 2.13 Removal of 1 Retro study OR 2.03 (for risk factor DM?)	No evidence of publication bias. All studies scored 7/8 on Newcastle-Ottawa scale for quality (what kind of quality?).

			or included cardiac				
O'Brien, et al 2013	Retrospective Secondary Analysis	III A	2,695 patients from 3 ICUs Surgical ICU Burn ICU Cardiovascular ICU Merged datasets from Talsma et al and intraop database.	Hypothesized intraoperative risk factors increased likelihood of postoperative new-onset PI. Retrospective review to characterize intraoperative risk factors associated with development of PI.	10.7% (288/2695)	Independent predictors: ASA score 4 or 5; Underweight BMI, noncardiac operation, history of CHF, renal disease, existing airway prior to OR	9.7% stg 2, 0.8% stg 3, 0.4% stg 4, 23, 0.9% DTI 3.3% US. Propensity matching of 122 cases: Intra-operative blood products (OR 1.71, 95S%CI, 1.03-2.84, p-0.04); Pts. With PI: 60 minutes longer OR time(non-significant finding)
Ettema et al, 2013	Systematic Review of Lit (PRISMA)	III A	23 Studies (strict Inclusion) All studies B- to A+ Quality Score	To provide an overview of both single and multi-component preadmission interventions designed to prevent single	No studies Identified that described PI prevention.	NA No studies with PI as outcome variable	Authors conclude no high-quality evidence to prevent PI to date.

				and multiple postoperative complications in older cardiac surgery patients.			
Hayes, et al, 2015	Retrospective, matched case-control.	III A	32,963 patients (Vanderbilt, USA) OR, ICU	To determine if time in the operating room increases risk of newly documented PI.	931/32,963 (2.8%)	OR for PI development and OR time: 1.1 <2hrs 1.2 >2, <4 1.6 >4, <6 6.4 >6 78% HAPU doc on POD3. 4.5% reported within 24hrs after OR.	NOTE: Pts with PI documented in first 24hrs deemed POA, but no description of pts admitted directly to OR, resulting in potentially missed PI.
Shen et al 2015	Retrospective Study with propensity score matching	III A	286 CT Surg Pts adults and peds (China)	To investigate the relationship between length of	16.4% (95% CI: 12.3-21.2) Peds 4.3%, Adults 18.8%	Age, Disease Category, Corticosteroids ($p<0.05$).	Time on CPB not sig. Sex, weight, introp vasoactive and post op vasoactive agents not sig.

			OR ICU	surgery and incidence of PI in cardiovascular surgical patients.			Length of Surgery sig diff between group with/without PI (p=0.03).
Borghardt, et al, 2015	Prospective Cohort Study	III B	77 patients from mixed ICU population (Brazil). ICU Mixed	Identify the incidence of PI and describe the factors associated with its development in adults hospitalized in ICU.	17 PI 22% (95% CI: 12.6, 31.5)	Sig values in bivariate analysis LOS>10 days (P-.000) CHF Yes: (P-.008) Death: (p-0.001) Braden Risk <11 (p.003)	5 CHF pts/4 developed PI 59% of PI positive pts died
Kang & Zhai, 2015	Meta-analysis of Surgical Patient PI risk and DM	I A (? Level of sig less since no RCT in analysis?)	13 Studies with 2367 patients and 12053 controls. Surgery types; Cardiac (4), General (5), Hip Fracture	To assess diabetes as a risk factor for PI in patients undergoing different types of surgery.	Pooled OR 1.74 (95%CI= 1.40-2.15, I^2=51.1%) Cardiac Studies:	OR of PI in DM patients significant in all 4 Cardiac Surgery Studies What was the OR	Restricted movement from cardiac assist devices (balloon pump, LVAD, and heart failure) considered to be contributing factors No increased PI incidence observed

			(2), LE Amp (2)		OR=2.0, 95%CI=1.42-2.82, I^2= 0%;		in pts undergoing Hip Surgery
Cox & Roche 2015	Retrospective correlational	III A	306 Patients 2 ICUs Medical-Surgical and Cardiac Surgery ICU	Examine associations between type, dose and duration of administration of vasopressor agents of PI in ICU patients in medical-surgical and CT surgery units and examine factor significantly predictive of development of PI.	13% (41/306)	39% of PI DTI; 56% sacrum 84% (257/306) Received norepinephrine. 37/41 (90% norepinephrine) Log regression predictors: 1. Arrest (B=1.359, p=0.05 OR 3.894, CI=0.998-15.118), 2. Mechanical ventilation longer than 72 hours (B=3.161; P<.001; OR=23.604,	Pts with PI had sig longer infusion times of vasopressin (32 vs 87 hours; p=0.005) longer infusion times of high dose vasopressin (20 vs. 57 hours, p=0.03). Pts receiving 2 pressors significant in PI pts (norepi and vasopressin (X^2=39.3, p<0.001) Longer infusion times at a dose at 0.03 U/min or higher may be "tipping point" for PI development.

						95%CI 6.427-86.668 3. Hours MAP less than 60mmhg while on pressor (B=0.092; P=0.01; OR=1.096; 95%CI= 1.020-1.178 4. Admin Vasopressin (B=1.572, P=0.004; OR 4.816; 95% CI 1.666-13.925 5. Cardiac diagnosis at ICU admission (B=-3.360, P=0.03; OR 0.035; 95%CI=0.002-0.764.	
Rao et al, 2016	Systematic Review	III A	12 Studies Mixed Population: Critical Care,	Identify risk factors associated with PI development among	Not reported	**PREOP RISKS** SCI (OR 16.8) HX PI (OR 13.51)	Noted absence of DTI discussion in the research for Cardiac Surgery Patients.

			Surgical ICU or Cardiac Surgery Populations OR/ICU Studies	critically ill, adult, cardiac surgery patients.		Skin prob in Pu areas (OR 4.7) HD 24hrs (OR 4.77) HD 48 hrs. (OR 9.43) Creatinine >3 mg/dl (OR 3.70) Limited Mobility (OR 2.27 and 4.42 based on 2 studies) Fecal INC (OR 3.27) Age (OR 1.03, 2.9, 5.38 in 3 studies) Vascular Disease (OR 2.95, 4.51, 1.80 in 3 studies) Anemia (OR 2.81) Severity of Illness (OR 2.49, 3.40, 2.32 in 3 studies). DM (OR 2.70, 1.85, 1.49 in 4 studies) Malnut (OR 1.61) Malig Tumor (OR 1.48)	Suggest “hypoxic-reperfusion” is linked to DTI and has not been adequately represented in the theoretical framework of PI development.

						Pain (OR 1.43) Gen Skin problem (OR 1.34) Low Preop Braden (OR 1.22, 1.21 in 2 studies) Low wt/BMI (OR 1.01, 1.03 in 2 studies) Admit Hgb (no OR listed) **INTRAOP** Friction/shear (OR 5.72, 1.72 in 2 studies) LOS > 3day (OR 2.76) Total # surgeries (OR 2.23) Total time in OR (OR 1.07) Hours in ICU (OR 1.01) **POSTOP**	

						Vasopressor (OR 1.02, 6.05, 8.11, 1.33 in 4 studies) Mech Vent (OR 4.82) Sedative drug (OR 1.61) Post op Steroids and Post op Braden (No OR listed).	
Robich, et al 2017	Retrospective	III A	N=588,417; n=4377 Never Events OR/ICU	Evaluated the nature, risk factors, and outcomes of never events following CABG, valve repair or replacement or thoracic aneurysm repair.	4% PI Stage ¾ over 8-year range (0% 2003-2007) (12% 2008-2011)	Risk factors reported for all possible never events. Pressure ulcers not reported individually. Never events significant for higher Mortality, LOS, Hospital Cost.	Sig risk factors of all never events matching previously reported PI risks: (weight loss, cancer, diabetes, CHF, Gender, Ethnicity, HTN, Age,) Coagulopathy)These were significant in bivariate and the first column in multivariate

Lu, et al 2017	Prospective Consecutive Cohort	III A	149 Patients (China) OR/ICU	To build a new nomogram score and test its calibration and discrimination power for predicting surgical PI in cardiovascular surgical patients.	24.8% (94% CI 18.1-32.6)	Sig level of <.10 for Log Reg model: Valvular Disease (p=0.063) CAD p<0.03; Wt (p< 0.091), Surgery duration p<0.036; Corticosteroids (p < ; OR for these factors?	94.6% Stage 1 PI, Rest Stg 2. Not significant: gender, wt, alb level, smoke status, DM, CPB duration, post op mech vent duration, vasoactive agents intra or post op were not different between PI/No PI (p>.10). Authors developed predictive nomogram with significant goodness of fit where by pts with probability scores greater than 0.25 should be considered high risk.
Kirkland-Kyhn, et al 2017	5-year Retrospective Descriptive	III B	119 patients (US) 7 ICUs (cardiac surgery, trauma surgery, burn surgery, med-	Identify common patient characteristics and factors that contribute to development	47 HAPU, 72 non-PU	Dialysis OR 4.0 (95%CI--.06-0.99, p=0.05) Shock state (yes/no) OR 10.0 (95%CI 0.025-0.43, p=0.002)	For every hour in surgery odds of DTI increased by 20%

			surgery, neurosurgery, medical, transfer ICU	of DTIs that evolved into stage 3, stage 3 and unstageable HAPU in ICU patients. Secondary purpose to define specific parameters for risk factors to identify patients at risk for HAPU within ICU Population.		DBP OR 0.93 (95%CI 0.88-0.99, p=0.02) Time surgery in Hours OR 1.20 (95% 1.07-1.33, p=0.001).	

Key to abbreviations in the table: ALB-albumin; CAD-Coronary artery disease; CPB-cardiopulmonary bypass; DBP-diastolic blood pressure; DM-diabetes mellitus; CT surg-cardiothoracic surgery; HAPU-Hospital acquired pressure ulcer; Hgb- Hemoglobin; HCT-hematocrit; HD-Hemodialysis; HTN-hypertension; ICU-Intensive Care Unit; INC-incontinence; intraop-intraoperative; LOS-Length of stay; OR-operating room; POD-Post operative day; SBP-systolic blood pressure; SCI-spinal cord injury; wt.-Weight

TABLE 3: Common Risk Factors of All Included Studies

MOST COMMON PREDICTORS IN STUDIES WITH MULTIVARIATE ANALYSIS											
ARTICLE	ASA Score	Age	DM	SBP <80, DBP<60	Arrest/MI	Cortico-steroids	Low BMI	OR TIME	Cardiac Dx/Dz Cat	Braden	Mech Vent
Li, et al, 2008			√								
Primiano, et al, 2011	√										
Ghavidel et al, 2012		√	√	√	√						
Liu, He & Chen, 2012			√								
O'Brien, et al 2013	√					√	√		√		√
Shen, et al 2015		√						√			
Borghardt, et al 2015									√	√	
Kang & Zhai, 2015			√								
Cox & Roche, 2015				√	√	√			√		√
Rao, et al 2016*	√		√			√	√	√		√	√
Lu, et al, 2017							√	√	√		
Kirkland-Kyhn, et al 2017				√	√			√			
Robich, et al 2017		√				√	√		√		
Chen et al 2018		√						√	√		

*Systematic Review

Abbreviations: ASA-Anesthesia Severity Assessment; DM-Diabetes Mellitus; SBP-Systolic Blood Pressure; DBP-Diastolic Blood Pressure; MI-Myocardial infarction; BMI-Basal Metabolic Index; OR-Operating Room; Dx-Diagnosis; Dz-Disease; Mech Vent-Mechanical Ventilation