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Assessment of the impact of oxandrolone on outcomes in burn injured patients

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ABSTRACT

The purpose of this study is to use a retrospective cohort of burn patients to evaluate the contribution of oxandrolone on burn care outcomes. Longitudinal clinical data is used to analyze outcomes from a new perspective. Our random-effects longitudinal regression analysis model used temporal clinical data to evaluate oxandrolone's impact on outcomes (oxandrolone/non-oxandrolone n=50/11, median length of stay [LOS]=42.2/39.3, mean weight (kg)=192.2/207.6, mean initial prealbumin (mg/dL) 10.1/7.5). The resultant predictive models ($p<0.001$) described how certain factors influence clinically significant outcomes via a robust data analysis method. LOS was predicted and extended by a greater magnitude of 3rd-degree versus 2nd-degree burns (1.01 versus 0.85 additional days for each %TBSA, $p<0.001$). Weight was decreased by LOS (145.2g lost per day, $p<0.001$). Oxandrolone improved prealbumin (3.503mg/dL increase, $p<0.001$) but instead did not influence patient weight ($p>0.05$) nor LOS (5.27days shortening, $p=0.361$). Prealbumin over time was also influenced by initial value (0.293mg/dL, $p=0.003$), LOS (0.072mg/dL increase per additional day, $p<0.001$), and the presence of inhalation injury (2.652mg/dL decrease if present, $p=0.009$). Oxandrolone appears to benefit anabolic protein production. It is difficult to isolate the role of oxandrolone on major outcomes due to the concomitant influence of other variables.

1. Introduction

Thermal injury causes the failure of the integumentary system. The destruction of this organ system produces a remarkable and complex environment of inflammation, immune suppression and physiologic stress. This translates into a state of hypermetabolism that is proportional to the severity of the burn [1,2]. Consequently, resting energy expenditure (REE) may increase beyond 200% of normal values in these patients [3].

Managing this increased REE in an effort to regulate hypermetabolism is a cornerstone of modern burn care. The natural course of a severe burn is an oscillation between states of profound anabolism and catabolism. When provided optimal nutritional support, the amount of time spent in productive anabolism is maximized [4]. If this support is not considered, the natural course of a burn injury leads to the body spending a disproportionate amount of time in a net catabolic state. This often results in a dramatic rate of weight loss. Oxandrolone has been suggested as one potential intervention. It may further counter-balance such catabolism

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[5] and offer other therapeutic benefits, including reduced weight recovery and wound healing times.

Oxandrolone is one of the original synthetic androgenic steroids and has been used in the clinical setting for decades. Dr. Demling with the Brigham and Women's Hospital Burn Center and David Herndon at the University of Texas Medical Branch Burn Center (UTMB) first published results showing that the use of oxandrolone significantly improved the weight gain recovery phase by shortening time to preinjury weight nearly twenty years ago [6].

Demling and UTMB groups have investigated the use of oxandrolone in burn patients quite extensively. Multiple studies have found that oxandrolone, when compared to other androgens, is the most efficacious in improving the basic outcomes of burn care [7,8]. Other studies have shown that oxandrolone improves the weight recovery time [9,10] and enhances the rate of wound healing [11]. These improvements were directly isolated from covariates by Hart's study on tracking protein kinetics over the course of care for pediatric burn patients. Hart's group confirmed that oxandrolone was beneficial in improving their length of stay (LOS) and wound healing as supported by the more favorable kinetic profile observed in the oxandrolone group [5].

Existing literature shows that oxandrolone indeed improves patient outcomes, albeit to a limited extent [12–16]. While some of this research included adults, the majority evaluated oxandrolone exclusively within pediatric populations. Miller and Btaiche's review noted that additional research in adult populations is needed, in addition due to the existing literature being largely comprised of studies with low sample sizes and being produced by only a few institutions [17]. A notable exception to this trend was a multicenter study led by Steven Wolf in adults where such a strong negative correlation between LOS and oxandrolone administration led to the early termination of the study's non-oxandrolone group [18]. The authors agree with Miller and Btaiche's conclusion and further note that these studies have narrow inclusion criteria and investigative measurements.

Previous studies have both supported and refuted oxandrolone's role in the overall improvement in care outcomes in the United States. Confounding nutrition and metabolic factors are likely implicated in these mixed results. These include but are not limited to rate of wound closure, optimization of quality, timing, and delivery of modalities of nutrients, improved infection control, and management of medical comorbidities. Much of the existing research on oxandrolone has focused on weight as a primary outcome over protein anabolism; studies succeeding in demonstrating a positive correlation between oxandrolone and weight are often of low effect magnitude. Matching and comparing subjects on the basis of solely oxandrolone is difficult due to the granular nature of the interpatient covariates, including differences in the mechanism of injury, prehospital care, and unknown medical comorbidities. Finally, a majority of the research evaluating oxandrolone has assessed usage within pediatric populations. Additional studies isolating the effect of oxandrolone versus the covariates of nutrition, metabolic, and injury dynamics are needed; especially in adult populations.

This retrospective analysis and case series review of recent clinical data from the authors' institution seeks to address these lapses within the literature. An alternative approach to collecting and analyzing clinical data is presented that allows metabolic parameters to be considered in enhancing data collaboration in multi-center studies and ultimately, may allow for tailored treatment programs on a patient-by-patient basis.

2. Methods

This was a retrospective chart review involving human subjects. The principles outlined in the Declaration of Helsinki were followed. Institutional review board (IRB) approval was sought and obtained (FWA #00006767; IRB #00000096). Since the data was retrospectively collected and its usage was of no risk to the subjects involved, informed consent was not obtained.

2.1. *Inclusion and exclusion criteria*

The inclusion criteria were age 18–70, total body surface area (TBSA) of ≥20%, admitted to University Medical Center Timothy J. Harnar Regional Burn Center from December 1, 2010 to August 1, 2016. Burns of the thermal (specific cases involved explosive agents, caustic agents, kinetic force, scalding, and or steam), chemical, and electrical type were included.

The exclusion criteria were subjects who did not initiate and/or terminate their burn care at University Medical Center Timothy J. Harnar Regional Burn Center (e.g. transferred), those with insufficient data in the medical record (e.g. no weight measurements available, missing TBSA assessment worksheets), those with breast, prostate, testicular carcinomas, or Stevens-Johnsons Syndrome/Toxic Epidermal Necrolysis etiologies.

Due to the nature of this regression analysis, subjects who died at any point during their stay are excluded, as the temporal format of this analysis cannot accommodate that outcome appropriately. Their death would be interpreted as an improved outcome within the model, as there would be fewer temporal data points. This analysis does not have the capability to differentiate between a subject's fewer data points being due to a shortened, successful LOS versus a stay that was shortened via death. For example, an oxandrolone-receiving patient with a 75% TBSA injury who was discharged at 45 days would be interpreted as an inferior outcome to a non-oxandrolone patient with a 75% TBSA injury who died on day 30 from sepsis. Likewise, third spacing of fluid associated with septic shock could lead to deceased subjects' end weights appearing superior to successful patients.

2.2. *Routine nutritional care & oxandrolone administration*

Caloric needs were calculated using the Irenton-Jones equation. Feeding protocol was started within 12 h of injury and within 6 h of arrival to the burn center for more than 95% of the patients. Patients are started at a trophic rate of 20cc per hour and escalated to estimated goal within 24 h, for more than 95% of the patients. Patients are overfed approximately 15% of estimated need to accommodate for stoppages in tube feeding secondary

to interventional therapies. The first prealbumin is drawn within 72h. After the first week, prealbumin is drawn twice a week, metabolic carts once a week, and urinary urea nitrogen (UNN) collected once a week. Oxandrolone was started day 1 of admission with 20mg orally administered once, daily.

2.3. How the impact of oxandrolone was assessed

In assessment of the impact of oxandrolone, the variables collected and controlled for were LOS, admit weight/BMI, discharge weight/BMI, prealbumin, whether or not oxandrolone was used, TBSA of both 2nd and 3rd degree burns as separately considered variables, age, whether or not there was inhalation injury (as documented by bronchoscopy evidence of pathology), and the number of surgical operations. The first prealbumin was drawn on average 3 days after admission. The regression models accounted for these factors to best match subjects between the oxandrolone and non-oxandrolone group based on the severity of their illness on admission.

2.4. Statistical analysis

Data quality control identified and excluded extraneous data points: daily clinical weights higher than 5% that of admission weight (likely due to transient fluid resuscitation), the exclusion of multiple weight measurements within a 24-h period, and exclusion of outlier data points for weight measurement. In total, these adjustments eliminated 46 of the 1142 data points collected for weight. The higher value of two present measurements would be taken, unless that value was greater than 10% of the previous available measurement. In such cases the lower value would be taken, since the higher value was likely due to measurement error. No prealbumin values were eliminated.

Variable distributions were inspected using histograms, box plots, and normality tests. Data were summarized using mean (standard deviation), median (interquartile range), and frequency (percentage) as appropriate. Differences between groups were calculated using Student's t or Wilcoxon rank-sum, and Fisher's exact tests for continuous, interval, and categorical variables respectively. Since LOS presented significant skewness and kurtosis, robust locally-weighted regression analysis was used to predict LOS from the aforementioned clinical predictors.

A random-effects longitudinal – or panel data – regression analysis model was used to predict change in weight from the aforementioned predictors, to account for the within-subjects effect due to the use of multiple records over time for each patient. The same method was used to predict change in prealbumin over time from the predictors, with the difference that admit weight was substituted by initial prealbumin. Significance level was set at 0.05. All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX) (Table 2).

3. Results

3.1. Differences in between groups at admission

Upon initial scan of the institution's internal data registry, 387 subjects met the described selection criteria. After actual extraction and verification of these records, 11 subjects not receiving oxandrolone, and 50 receiving oxandrolone, were identified and underwent analysis. Table 2 describes the sample characteristics with subjects grouped by their oxandrolone administration status. No statistically significant differences were found at admission between subjects who did and did not receive oxandrolone treatment.

3.2. Length of stay predictors

Each subject had some amount of a 2nd degree TBSA injury (oxandrolone median=12%; non-oxandrolone median=20%) and with the exception of one non-oxandrolone patient, all had some amount of a 3rd degree TBSA injury (oxandrolone median=21%; non-oxandrolone median=14%). The median LOS for the non-oxandrolone group versus the oxandrolone group was not statistically different (39.3 days versus 42.2, $p=0.881$, Table 2). Table 3 details the association of the discussed predictors with LOS. This relationship was very loose, with the raw analysis finding none of these predictors to influence LOS ($p>0.05$). Oxandrolone was not found to influence LOS, see confidence intervals of adjusted versus unadjusted data in Table 3. Finally, inhalation injury did not show any clear effect on LOS (Table 3). However the regression analysis was adjusted, to where the influence of these individual predictors were each considered against the acknowledgement that there was a concomitant influence from the other predictors, significant results were identified. A robust regression function beyond the scope of this paper explains approximately 33% of the described variability. The size of the burn, inclusive of both 2nd and 3rd degree TBSA burns, were predictive of a longer stay ($p<0.001$). As reflected by the coefficients in the 'adjusted' column of Table 3, a greater amount of 3rd degree (1.01) versus 2nd degree (0.85) burns was found to increase patient LOS.

To predict the LOS (days) of a patient based on their burn injury ($TBSA_{3rdDegree}$ and $TBSA_{2ndDegree}$), we could use the following formula[1]:

$$LOS = 3.26 + 1.01\,(TBSA_{3rdDegree}) + 0.85\,(TBSA_{2ndDegree}) \quad (1)$$

3.3. Weight predictors

Each patient had on average 12 weight assessments (median=14, max=78, minimum=4). Using a longitudinal regression model ($p<0.001$) we were able to predict 95% of weight variability over time (Table 4), which accounted for 98% of between-subjects, and 32% of within-subject variability respectively. Only the number of days that had passed since the subject was admitted ($p<0.001$) and admit weight ($p<0.001$) were statistically significant predictors of weight over time. Other predictors, including oxandrolone administration or inhalation injury, and confounding factors such age, TBSA, and BMI did not show any statistically significant predictive value on weight change. While a detailed explanation is beyond the scope of this paper; the statistical model was

[1] LOS=Length of stay (days); $TBSA_{3rdDegree}$=The 3rd degree burn extent expressed as a whole number; $TBSA_{2ndDegree}$=The 2nd degree burn extent expressed as a whole number.

Table 1 – Summary of referenced studies on oxandrolone's role on clinical outcomes.

	n (Oxa/Non)	Age (mean)	Sex (M/F)	TBSA (mean)	LOS (mean)	Prealbumin baseline	Prealbumin post treatment	Weight change (Oxa/Non)
Hart et al. [5]	14 (7/7)	Oxa: 8.0±1.9 Non: 7.7±2.3	Oxa: 4/3 Non: 3/4	Oxa: 42±9 Non: 42±5	Oxa: 18±9.5 Non: 16±13.5	Oxa: 8.5±1.4 Non: 12.4±11	Oxa: 12.7±0.9 Non: 16.4±1.1	Oxa: −0.3±0.7 kg Non: −1.1±0.7 kg
Demling and DeSanti [6]	Yng: 25 (13/12)	Yng: 34±5		Yng: 47±10	Yng: 21±6			Yng
	Old: 15 (8/7)	Old: 60±5		Old: 36±5	Old: 32±8			Oxa: +79%±4 Non: +59%±9 Old Oxa: +76%±5 Non: +51%±6
Demling [8]	40 (16/24)	Oxa: 49±15 Non: 40±13	Oxa: 13/5 Non: 16/8	Oxa: 56±15 Non: 39±12	Oxa: 34±8 Non: 35±9			Oxa: −3.0±1.2 kg Non: −8.0±2.1 kg
Demling and Orgill [11]	20 (11/9)	Oxa: 49±13 Non: 44±6		Oxa: 53±9 Non: 49±8	Oxa: 29±8 Non: 35±9			Oxa: −3.0±1.9 kg Non: −8.0±3.1 kg
Jeschke et al. [13]	235 (45/190)	Oxa: 8.0±0.7 Non: 7.7±0.4	Oxa: 31/14 Non: 112/78	Oxa: 58±2 Non: 55±2	Oxa: 28±2 Non: 31±2	Oxa: 9.5[a] Non: 7.5[a]	Oxa: 20.3[a] Non: 14.5[a]	Oxa: +8%[a] Non: −9.5%[b]
Li et al. [14]	806 (192/614)				AP: Oxa had shorter LOS by 3.02±0.64 vs. Non.[c] RP: Oxa had shorter LOS by 6.45±2.24 vs. Non.		AP: Oxa had less net weight loss 5.0 ±1.3 kg vs. Non.[c] RP: Oxa increased weight per week 0.86±0.10 kg vs. Non.[d]	
Wolf et al. [18]	81 (46/35)	Oxa: 39±2 Non: 40±3	Oxa: 35/11 Non: 26/9	Oxa: 35±2 Non: 36±2	Oxa: 31.6±3.1 Non: 43.3±5.3			

Oxa = patient group receiving oxandrolone; non = patient group which did not receive oxandrolone; TBSA = total body surface area, percentage; LOS = length of stay, in days; prealbumin expressed as mg/dL; weight change = amount of weight change, expressed as either mean kilogram change or mean percentage change; Yng = study group ages 18-40; old = study group ages 55 and older; AP = acute phase and RP = rehabilitation phase, see footnote c.

[a] This study estimated prealbumin from patient charts.

[b] This is the percentage change in lean body mass.

[c] Acute phase is defined as timeframe from admission to acute hospital to discharge to inpatient rehabilitation center. Rehabilitation phase is defined as the timeframe from admission to inpatient rehabilitation center to discharge.

[d] Weight per week was reported; actual weight was not reported.

Table 2 – Sample description. Sample sizes for LOS-to-TBSA (2nd degree) for No/Yes were 10/44 and for (3rd degree) were 8/39.

	Received oxandrolone		p
	No (n = 11)	Yes (n = 50)	
Admit weight (kg), mean (SD)	94.17 (24.99)	87.18 (21.82)	0.352
Admit BMI (kg/m^2), mean (SD)	30.5 (6.9)	28.2 (6.4)	0.300
Initial prealbumin (mg/dL), mean (SD)	7.5 (3.1)	10.1 (5.2)	0.107
Age (years), mean (SD)	42.6 (18)	40.6 (15.3)	0.702
TBSA total, median (IQR)	22 (22–37)	36 (29–48.5)	0.306
TBSA 2nd degree, median (IQR)	20 (0.25–22)	12 (1–29.5)	0.735
TBSA 3rd degree, median (IQR)	14 (0–20.5)	21 (5–32)	0.326
Length of Stay (days), median (IQR)	39.3 (23.7–57.9)	42.2 (25.9–67.8)	0.881
LOS-to-TBSA (total), median (IQR)	1.87 (0.78–1.89)	1.1 (0.67–2.03)	0.348
LOS-to-TBSA (2nd degree), median (IQR)	2.66 (1.52–7.16)	2.55 (1.27–10.4)	0.894
LOS-to-TBSA (3rd degree), median (IQR)	1.87 (1.15–2.51)	1.87 (1.28–3.35)	0.258
LOS-to-TBSA (total) ≤ 1, n (%)	8 (72.7)	32 (64)	0.733
LOS-to-TBSA (2nd degree) ≤ 1, n (%)	4 (40)	14 (31.8)	0.715
LOS-to-TBSA (3rd degree) ≤ 1, n (%)	1 (12.5)	14 (35.9)	0.406
Inhalation Injury, n (%)	5 (45.5%)	18 (36%)	0.733
# Surgical operations, median (IQR)	6 (3–14)	9 (6–17)	0.605

SD = standard deviation; IQR = interquartile range; BMI = body mass index; LOS = length of stay; TBSA = total body surface area; p-values were calculated using Student's *t* test, Wilcoxon sum-rank test, and Fisher's exact test. IQR approximates the middle of the data set, inside of which 50% of data points under an ideally distributed/bell-curve will fall. The left number is the upper end of the first quartile, and the right number is the lower end of the third quartile. A narrower IQR indicates that more data points were close to the reported median, while a wider IQR indicates that there was more extreme variation from the reported median.

Table 3 – Length of stay (days) regression analysis.

	Unadjusted				Adjusted		
	R^2	Coef.	95% CI	p	Coef.	95% CI	p
Oxandrolone	0.002	−2.17	−14.67 to 10.33	0.729	−5.27	−16.73 to 6.19	0.361
TBSA 2nd degree (%)	0.027	0.22	−0.12 to 0.55	0.202	0.85	0.42 to 1.29	<0.001
TBSA 3rd degree (%)	0.053	0.31	−0.03 to 0.65	0.074	1.01	0.58 to 1.43	<0.001
Age (years)	0.007	0.10	−0.21 to 0.41	0.514	0.26	−0.05 to 0.56	0.096
Inhalation injury	0.023	5.64	−3.98 to 15.27	0.245	−1.49	−10.93 to 7.95	0.753
Admit Weight (kg)	0.001	−0.02	−0.24 to 0.19	0.833	−0.15	−0.58 to 0.28	0.479
Admit BMI (kg/m^2)	<0.001	0.05	−0.70 to 0.79	0.899	0.12	−1.35 to 1.59	0.873
Constant					3.26	−25.3 to 31.83	0.820

TBSA=total body surface area; BMI=body mass index.

Table 4 – Longitudinal regression analysis of weight change over length of stay.

	Initial model (R^2=0.95)			Simplified model (R^2=0.95)		
	Coef.	95% CI	p	Coef.	95% CI	p
Day since admission	−0.15	−0.16 to −0.13	<0.001	−0.15	−0.16 to −0.13	<0.001
Admit weight (kg)	0.97	0.89-1.05	<0.001	1.00	0.97–1.04	<0.001
Oxandrolone	−0.26	−2.31 to 1.79	0.803			
Admit BMI (kg/m2)	0.13	−0.12 to 0.39	0.309			
Age (years)	0.00	−0.05 to 0.05	0.977			
TBSA 2nd degree (%)	−0.03	−0.1 to 0.05	0.502			
TBSA 3rd degree (%)	0.01	−0.07 to 0.08	0.860			
Inhalation Injury	0.41	−1.23 to 2.05	0.621			
Constant	−0.18	−5.1 to 4.73	0.941	0.38	−2.63 to 3.38	0.805

simplified via a mathematical approach to eliminate extraneous data and allowed the regression model to focus on the most significant factors. After simplifying the model, the same explanatory power was kept (R^2=0.95 overall, 0.98 between, 0.32 within).

To predict the weight (kg) of a patient at any time ($Weight_{Day}$), we could use the following formula[2]:

$$Weight_{Day} = 0.3783 + 1.0039\,(Weight_{Admit}) - 0.1452\,(Day) \quad (2)$$

3.4. *Prealbumin predictors*

Prealbumin is a marker of hepatic protein anabolism with accepted clinical utility that can describe patients' response to nutrition regiments, when trended. Increasing values indicate protein anabolism. Each patient had on average 7 prealbumin values (median=7, max=58, minimum=1). The statistically significant ($p<0.001$) longitudinal regression model predicted 27% of prealbumin variability over time (Table 5), which accounted for 34% of between-subjects' variability, and 19% of within-subject variability. Days elapsed since admission ($p<0.001$), initial prealbumin levels ($p=0.003$), and oxandrolone administration ($p=0.01$) were significant predictors of prealbumin increase, while inhalation injuries predicted lower levels over time ($p=0.009$). The regression model including just significant predictors had approximately the same explanatory power (R2=0.26 overall, 0.49 between, 0.19 within).

Prealbumin levels (mg/dL) of a patient at any time (PA_{Day}) could be predicted as[3]:

$$PA_{Day} = 8.077 + 0.293\,(PA_{Initial}) + 0.072\,(Day) + 3.503\,(Oxa=yes) - 2.652\,(Inh=yes) \quad (3)$$

This formula demonstrates that prealbumin was positively influenced by the admission prealbumin, the length of stay, and if oxandrolone was given. Prealbumin was negatively influenced if there was evidence of inhalation injury.

4. Discussion

Nutrition support of a burn patient is essential to improving care outcomes by way of overcoming burn hypermetabolism. Besides providing adequate delivery of nutrients, medications such as oxandrolone may help.

The clinical outcomes evaluated against LOS were selected due to both their incorporation in frailty scores used to clinically predict mortality [19] and traditionally accepted

[2] $Weight_{Admit}$=Weight (kg) of patient at admission; Day=time (days) since admission; $Weight_{Day}$=Predicted weight (kg) on a particular day since admission.

[3] $PA_{Initial}$=Initial prealbumin level collected within the first 3 days after admission. Day=time (days) since initial prealbumin value; Oxa=patient on oxandrolone treatment. Inh=patient had inhalation injury; 1=yes, 0=no. Per bronchoscopy evidence; severity not graded. PA_{Day}=Predicted prealbumin value on a particular day since initial prealbumin assessment.

Table 5 – Longitudinal regression analysis of prealbumin change over length of stay.

	Initial model (R^2=0.27)			Simplified model (R^2=0.26)		
	Coef.	95% CI	p	Coef.	95% CI	p
Day since initial value	0.07	0.05–0.09	<0.001	0.07	0.06–0.09	<0.001
Initial prealbumin (mg/dL)	0.32	0.12–0.51	0.002	0.29	0.10–0.49	0.003
Oxandrolone	3.44	0.74–6.14	0.012	3.50	0.85–6.15	0.010
Admit BMI	0.11	−0.03 to 0.24	0.126			
Age	0.01	−0.04 to 0.07	0.659			
TBSA 2nd degree (%)	−0.03	−0.11 to 0.06	0.509			
TBSA 3rd degree (%)	0.01	−0.05 to 0.08	0.723			
Inhalation injury	−2.93	−5.11 to −0.74	0.009	−2.65	−4.65 to −0.66	0.009
Constant	4.68	−0.53 to 9.89	0.078	8.08	5.24–10.92	<0.001

utility. The models separately considered 2nd degree and 3rd degree TBSA values; the latter depth poses substantial added challenges with healing, desiccation, rehabilitation, and infection risk compared to the former. As previously mentioned, the LOS-to-TBSA median value for the non-oxandrolone group was 1.87 versus 1.10 for the oxandrolone group but was not statistically significant ($p>0.05$, Table 2). Despite these findings, a strong argument can be made for a cost-benefit analysis approach. This statistical model equally weighs, irrespective of cost, the value of a day in a United States Burn Intensive Care Unit (BICU) versus the use of a drug brought to market in the 1960s. The difference in cost between the two is glaring. From a pragmatic approach, the suggestion that there may be a cost reduction of 1.10 days spent in the BICU per 1% TBSA from 1.87 overwhelmingly supports the use of oxandrolone to reduce BICU LOS, saving many healthcare dollars per burn patient (Fig. 1).

The method used to collect and process the data, incorporating time, allowed the creation of analytical models. Formulas with predictive capacity were made, approximating LOS against 2nd degree and 3rd degree burns and weight against LOS. Additionally, prealbumin can be compared against the initial value, LOS, oxandrolone administration status, and the presence of inhalation injury. For example, for a patient with a 3rd degree TBSA injury of 21% and a 2nd degree TBSA injury of 12%, we would predict that the LOS=3.26+1.01(21)+0.85(12)=34 days. Likewise, on the 20th day of a hospital stay of a 100 kg patient, we would predict that the $\text{Weight}_{\text{Day}}$=0.3783+1.0039(100)−0.1452(20)=97.86 kg. Finally, the prealbumin value of a patient whose initial prealbumin value was 10.1, on day 12 of admission, who did receive oxandrolone, but did not have an inhalation injury, would be predicted to be PA_{Day}=8.077+0.293(10.1)+0.072(12)+3.503(1)−2.652(0) =15.40 mg/dL.

Theoretically, the formulas can approximate a real subject's LOS, weight, and prealbumin values in the same way.

It was our expectation that this non-oxandrolone group would demonstrate greater weight loss over time. The main benchmarks, length of stay and subject weight ($p>0.05$, Table 3), were not influenced by oxandrolone. Still, oxandrolone demonstrated a strong benefit for the protein anabolism state; prealbumin values for subjects receiving oxandrolone were 3.503 mg/dL at any given time than non-oxandrolone patients (Formula (3)).

Histogram evaluation demonstrated that more subjects in the oxandrolone group (yes) had longer lengths of stay than those in the non-oxandrolone group (no). This difference in length of stay (42.2 days versus 39.3 median LOS) was not statistically significant (Table 3). The admission weights show a similar trend, with oxandrolone group patients having a wider range and lower nadir for admission weight. Table 1 describes a lower median number of surgical operations required by the non-oxandrolone group (6 operations) versus the oxandrolone group (9 operations). The higher number in the latter is supported by an equally narrow but more severe interquartile range (3–14 operations, versus 6–17; $p=0.605$). A similar argument is made for the size (total TBSA 22% versus 36%; $p=0.306$) and depth (2nd versus 3rd degree; see Table 2) of the median burn experienced by subjects in each group. There was both a higher mean and broader range of TBSA values for the oxandrolone group; their distribution is less uniform than that of the non-oxandrolone group. This is further demon-

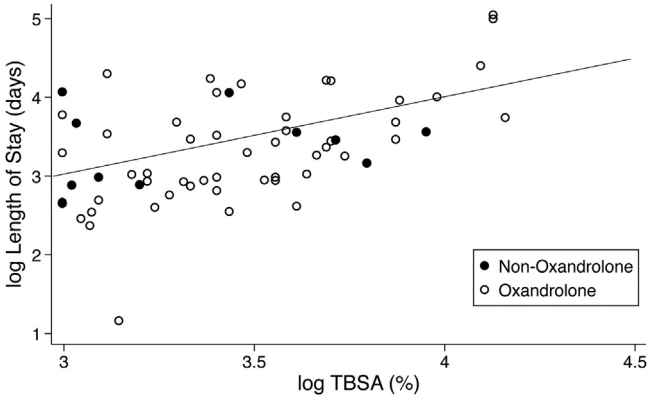

Fig. 1 – Length of stay in days against TBSA on a logarithmic scale, and a line showing the ideal "1 day stay per 1% TBSA" recovery pace. Those subjects above this line represent superior performance to the clinical axiom, a faster rate than 1 day per 1% TBSA, whereas those below the line perform worse. The LOS-to-TBSA median value for the contrast group was 1.87 versus 1.1 for the oxandrolone group. While this difference was statistically insignificant ($p=0.348$, Table 2), it demonstrates that neither group met the benchmark, but that the oxandrolone group recovered at a faster rate.

strated by two outliers in the oxandrolone group with a length of stay approximately 152 days. Consequently, it is possible that the oxandrolone group was more severely injured than the non-oxandrolone group. Better outcomes were nonetheless often seen at the granular, patient-by-patient level in the oxandrolone group.

There are inherent differences between our subject groups. Therefore, type II error is similarly implied at the macroscopic level, with oxandrolone having a positive influence and inhalation injury having a negative influence on prealbumin values, yet neither appearing to influence weight or length of stay. Published evidence supports nutritional status' influence on care outcomes, and prealbumin is a valid measure of that status. We failed to reject the null hypothesis, implying there is no difference between the outcomes of the non-oxandrolone and oxandrolone groups on the basis of oxandrolone. Type II error would explain the inaccurate hypothesis test result. These effects may be amplified with larger, more uniform data sets that allow closer matching of covariates, including frailty and injury severity scorings as well as the extent and mechanism of injury. Much of the existing research on oxandrolone has focused on weight as a primary outcome over protein anabolism. Studies succeeding in demonstrating a positive correlation between oxandrolone and weight are often of low effect magnitude. In conjunction with the previously conducted research on the mechanism of action of oxandrolone, clearly demonstrating enhanced protein utilization by hepatocytes to facilitate anabolic processes, it may be more appropriate to consider and quantify these underlying metabolic processes. Evaluating nutrition status and inflammation status over indistinct weight gain will best describe the healing course of the burn patient; allowing for better comparison of data across multi-center studies and to ultimately tailor treatment programs to individual patients.

The longitudinal analysis underlying this research demonstrates the utility of tracking nutrition parameters in both research and clinical care. Modern electronic medical record systems and nursing protocols allow for large amounts of data to be collected. This can be used to optimize care by adjusting caloric requirements, monitoring catabolism status, and predicting sepsis risk in real time, among other considerations. Future prospective studies should take advantage of such protocols and longitudinal analysis. As the covariates in care outcomes are differentiated by such future research, the same approach can be used to apply machine learning models to provide better recommendations for adjusting patient care in a continuous, evidence-based manner. Such learning models could allow providers to detect and intervene on complications, prior to their clinical manifestations.

4.1. *Limitations*

The sample size was small and unbalanced. For that reason, despite the clinical significance and novelty of our approach to the problem, some differences between groups at admission were likely not detected. Although the regression methods used in these analyses are capable of accommodating deviation from normality and autocorrelation issues, the results should still be interpreted with caution. As in any retrospective analysis involving chart review, the information in the medical records might have inaccuracies or missing values. Clinical limitations including bandage changes, bed scale malfunctions, nursing and unit operational capacities can be potent influences on retrospective analysis. The peak in weight due to fluid infusion was not properly determined from the records. An arbitrary yet conservative cutoff was required to contrast this source of variation. The initial prealbumin values might not reflect the patient's status at admission, since these values were recorded on average three days after admission.

4.2. *Conclusion*

Temporal data set analysis offers a higher resolution of the relationship between clinical predictors and outcomes. Advanced statistical methods allowed an optimized yet limited interpretation of the effect oxandrolone had on outcomes in this burn center. Oxandrolone improved prealbumin levels, suggesting that its use suppresses catabolism. Literature clearly supports that accomplishing the latter improves burn patient outcomes [20–22]. While not statistically significant, a decrease in LOS was noted with the use of oxandrolone (5.27 days shortening, $p=0.361$). In consideration of these factors and the previous discussion, it is most likely that a significant difference in hard outcomes between the oxandrolone and non-oxandrolone group was not identified due to a very limited data set, rather than oxandrolone having no influence on those outcomes. The failure to reject the null hypothesis in the oxandrolone group for more critical measures of patient outcomes like weight and length of stay must be considered against the subclinical but significant finding of an influence on prealbumin. The data in hospital databases is a powerful tool for studies that could give basis for higher evidence studies. In consideration of this, alongside other sub-significant correlates and data patterns described, this study provides ancillary evidence supporting the need for a large, multi-center prospective study to better define what role oxandrolone should play in adult burn care.

Conflict of interest

We have no conflicts of interest to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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