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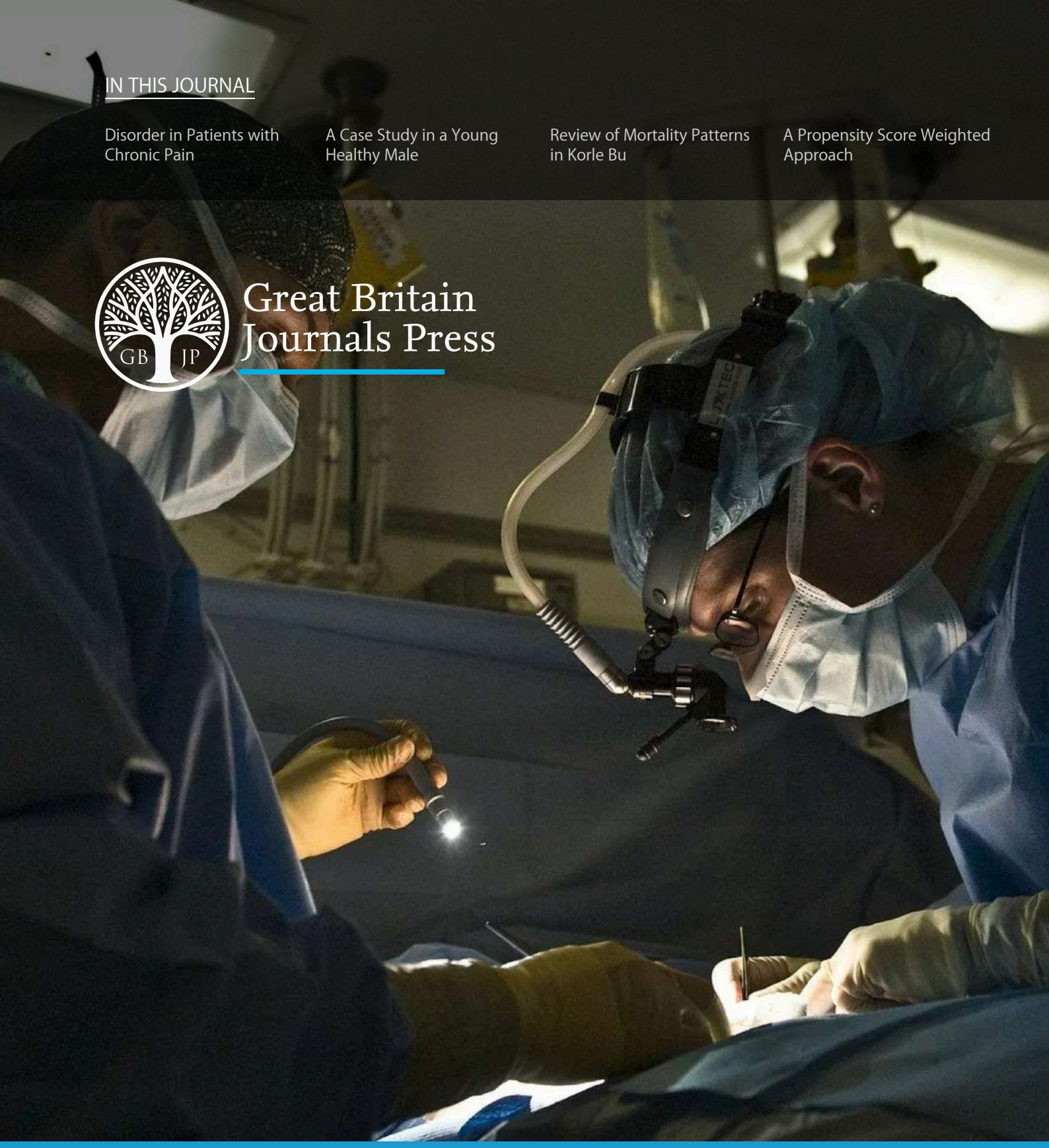

Great Britain Journals Press

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London Journal of Medical & Health Research

Volume 25 | Issue 6 | Compilation 1.0

COMPILED IN UNITED KINGDOM

ENGLISH

LONDON JOURNAL OF MEDICAL AND HEALTH RESEARCH

Volume 25 | Issue 6 | Compilation 1.0

PUBLISHER

Great Britain Journals Press
1210th, Waterside Dr, Opposite Arlington Building, Theale, Reading
Phone:+444 0118 965 4033 Pin: RG7-4TY United Kingdom

SUBSCRIPTION

Frequency: Quarterly

Print subscription
$280USD for 1 year
$500USD for 2 year
(*color copies including taxes and international shipping with TSA approved)*
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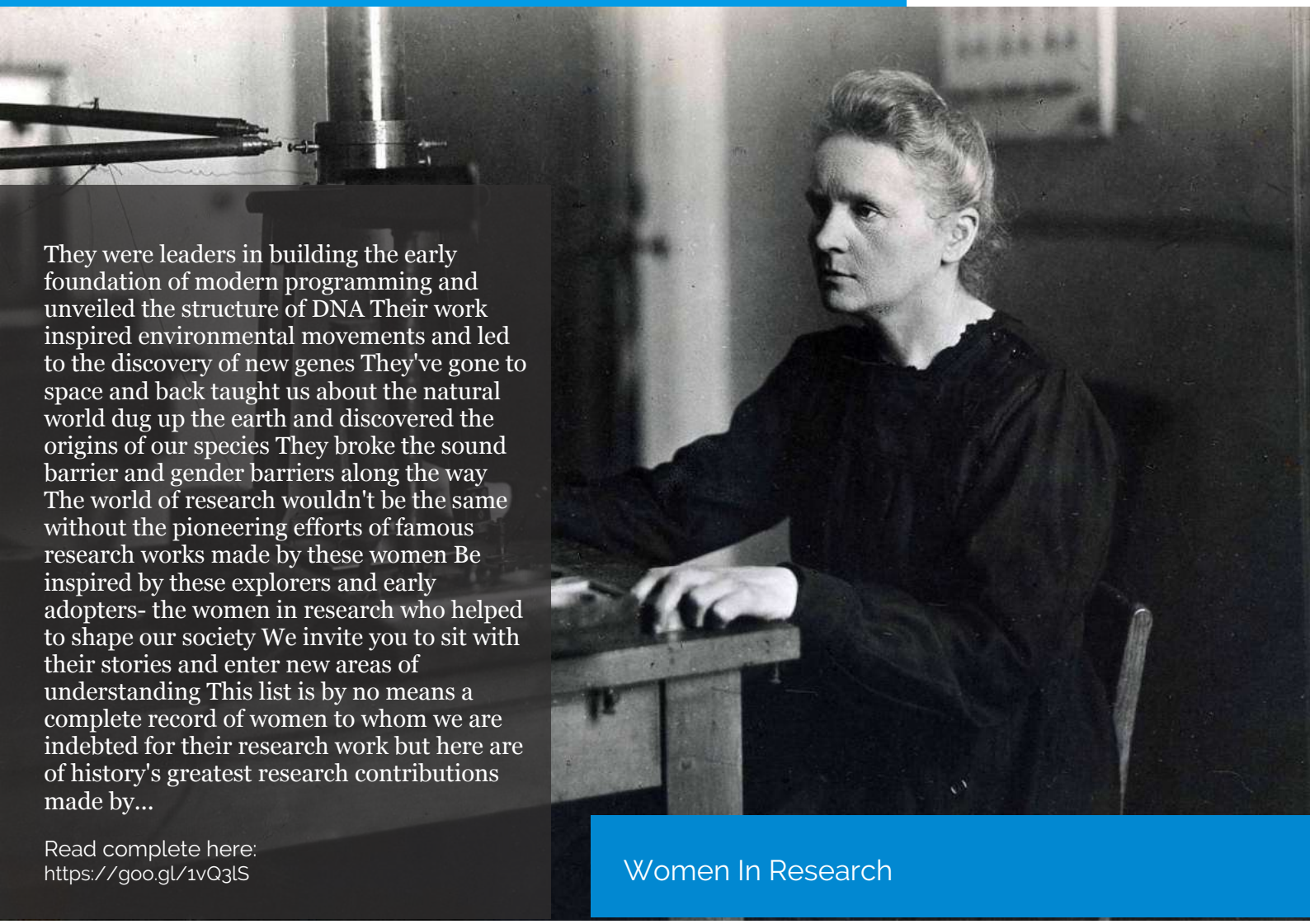

They were leaders in building the early foundation of modern programming and unveiled the structure of DNA Their work inspired environmental movements and led to the discovery of new genes They've gone to space and back taught us about the natural world dug up the earth and discovered the origins of our species They broke the sound barrier and gender barriers along the way The world of research wouldn't be the same without the pioneering efforts of famous research works made by these women Be inspired by these explorers and early adopters- the women in research who helped to shape our society We invite you to sit with their stories and enter new areas of understanding This list is by no means a complete record of women to whom we are indebted for their research work but here are of history's greatest research contributions made by...

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Predicted Healthcare Demand and Health Inequalities among Brazilian Adult Population: A Propensity Score Weighted Approach

Dr. P. Olivares-Tirado & Dr. R. Zanga

ABSTRACT

The aim is to analyse how specific socio- demographic and health factors influence healthcare demand, considering the socio-economicsocio-economic diferences in Brazil's adult population. The study focused on "expressed demand", i.e., an individual's need for healthcare services and their ability to seek care. Overall, the Brazilian adult population had a 22.1% probability of requiring medical care within two weeks before the survey. An increasing gradient was observed from the poorest to the wealthiest deciles, with the wealthiest group having a 40% higher healthcare demand than the poorest. The main predisposing, enabling and need factors analysed were relevant in determining healthcare demand; however, they are strongly influenced by income disparities.

Keywords: adult people, healthcare demand, income inequalities, propensity score, health policy.

Classification: NLM Code: WA 30.5, W 84.6, WA 300

Language: English

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Predicted Healthcare Demand and Health Inequalities among Brazilian Adult Population: A Propensity Score Weighted Approach

Dr. P. Olivares-Tirado[α] & Dr. R. Zanga[σ]

ABSTRACT

The aim is to analyse how specific socio-demographic and health factors influence healthcare demand, considering the socio-economicsocio-economic diferences in Brazil's adult population. The study focused on "expressed demand", i.e., an individual's need for healthcare services and their ability to seek care. Overall, the Brazilian adult population had a 22.1% probability of requiring medical care within two weeks before the survey. An increasing gradient was observed from the poorest to the wealthiest deciles, with the wealthiest group having a 40% higher healthcare demand than the poorest. The main predisposing, enabling and need factors analysed were relevant in determining healthcare demand; however, they are strongly influenced by income disparities. In the Brazilian context of a universal and free access healthcare system, a significant gap remains in healthcare demand due to income distribution, which disproportionately affects there is still a significant gap in healthcare demand through income distribution to the detriment of the poorest groups. Future research should focus on the impact of private health insurance on healthcare demand and spending. Monitoring the impact of private health insurance on healthcare utilisation is essential to ensure that provider profits do not influence healthcare demand.

Keywords: adult people, healthcare demand, income inequalities, propensity score, health policy.

I. INTRODUCTION

Healthcare demand analysis has various applications, including identifying factors that affect access to healthcare services, healthcare utilisation, utilization, and patient perceptions of healthcare quality. It can also reveal which social groups are excluded or delayed in receiving essential healthcare services due to poverty or other factors. This evidence can help policy makers address issues of efficiency and equity in healthcare systems (Mwabu, 2008; Rodriguez Santana et al., 2023).

Healthcare demand refers to the individual's decision to seek and pay for healthcare, influenced by their perception of health, socioeconomic status, cultural factors, and beliefs (Ghorbani, 2022; Levesque et al., 2013). Factors such as financial resources, education level, risk attitude, time costs, availability, accessibility, and quality of healthcare services affect healthcare demand (Mwabu, 2008).

Access to and utilisation of healthcare are two Critical factors related to healthcare demand. However, access is a complex concept that involves both supply and demand factors, while utilisation reflects the satisfaction of supply and demand factors, while utilisation utilization reflects satisfied and observed demand (Adhikari, 2011; Levesque et al., 2013). Simply measuring utilisation to define access overlooks other crucial factors such as care quality and cultural and financial barriers that contribute to inequalities (Allin et al., 2007). The demand for healthcare is influenced by both the needs of patients and the availability of healthcare services. Healthcare services encompass goods and services that maintain, improve, or restore health, possessing specific characteristics and unique qualities (Ghorbani, 2022).

From an economic perspective, the demand for healthcare is determined by the perceived benefits and the cost of accessing care (Rodriguez Santana et al., 2023). Individuals aim to maximise healthcare benefits within their budget constraints, but limited information about healthcare affects their ability to optimise benefits (Mwabu, 2008). This study examines expressed demand, which refers to an individual's need for health services and their ability to access care.

The Brazilian Unified Health System, a taxpayer-funded public health care system, offers free services to all residents (Costa, 2017). However, around 22% of the population holds private health insurance, allowing access to private healthcare providers (OECD, 2021). On the other hand, Brazil is experiencing a demographic transition with a rapidly ageing population (Demográfica, 2018a; OECD, 2019; Veras & Oliveira, 2018), which is also occurring with an epidemiological transition and significant socioeconomic and territorial inequalities (Lima-Costa et al., 2018; Programme, 2022). By 2043, 25% of Brazil's population is estimated to be over 60 years old (Demográfica, 2018b). Growth in non-communicable diseases, disability, rising obesity rates, physical inactivity, and other unhealthy lifestyles affects people of all ages but is more frequently associated with older and socially disadvantaged groups (OECD, 2021)

The study aims to analyze how sociodemographic and health factors affect healthcare demand in Brazil's adult population while accounting for socioeconomic differences. Understanding the impact of socioeconomic disadvantage on healthcare demand among vulnerable populations helps promote a comprehensive discussion on health inequalities.

II. MATERIALS AND METHODS

A cross-sectional study was conducted using data from the 2019 Brazilian National Health Survey (PNS 2019), which surveyed 275,323 individuals aged 15 years 2019-PNS), which surveyed 275,323 individuals aged 15 years or older. The survey was conducted using smartphones between August 2019 and March 2020, achieving a household response rate of 93.6% (Pesquisa Nacional de Saúde 2019, 2020).

The study included data from 62,454 people aged 18 or older who were considered competent to respond and answered the healthcare utilisation module.

The outcome variable was self-reported healthcare demand, obtained through the question: "In the last two weeks, did you require a place, service, or health professional for care related to your health?" For the analyses, a binary variable was arranged; those who answered “yes” were considered the interest group, and those who answered “no” were considered the reference group.

The 2019-PNS survey collected detailed information on geographic, sociodemographic and health factors. Covariates were selected based on their association with the treatment variable. Because previous research had found that sleep disturbance patterns experienced by socioeconomically disadvantaged groups are associated with adverse health outcomes and increased healthcare utilisation n and expenditures (Grandner et al., 2016; Huyett & Bhattacharyya, 2021), sleep disturbances were included in the analysis.

The study included several dichotomous variables, such as sex(1=woman), marital status (1=married), residence area (1=urban), working (1=yes), health insurance (1=yes) dental insurance (1=yes), social participation (1= participation more than twice time a month), alternative medicine use (1=yes), and tobacco smoking (1=yes).

The covariates,; including sex, marital status, residence area, employment status, health insurance, dental insurance, social participation, alternative medicine, and tobacco smoking, were included as dichotomous variables. The following covariates were included as categorical variables: age, region of residence, education level, self-rated health status (SRH), chronic diseases, sleep disturbances, physical activity, sedentary behaviour, and frequency of drinking alcohol. For details about categories and reference groups of these covariates, see Table 1.

The income deciles were included in the model as a discrete covariate. The availability of doctors obtained from the Federal Council of Medicine and the University of São Paulo data, was considered to adjust for the supply side (Scheffer, 2020). The distribution of doctors was assigned according to the capital areas or municipalities of each State, and the rate of doctors,was calculated per 1,000 inhabitants. The final regression model employed the product of sampling weight and propensity score weight to enhance both internal and external validity, thereby facilitating inferences about the population (Dugoff et al., 2014; Guo et al., 2020). The sample weight was calculated for the selected residents and calibrated for sex and age based on population projections.

A multistep approach was used to predict healthcare demand probabilities. Firstly, a multicollinearity diagnostic was conducted on the variables. Secondly, logistic regression was used to estimate a propensity score model for covariate adjustment. Thirdly, the propensity score balance was assessed across the treated and comparison groups by computing standardised differences using *the pbalchk* command (Garrido et al., 2014; Granger et al., 2020). Fourthly, individuals' propensity scores were weighted using inverse probability treatment weighting to ensure confounder similarity in the treatment and comparison groups (Olmos & Priyalatha, 2019). Fifthly, a logistic regression model including the product of the sampling and propensity score weights was run for healthcare demand, and the outcome probability was estimated using the logit post-estimation command "pr." Finally, the average probabilities for healthcare demand were calculated across income deciles for relevant covariates.

The statistical analysis was conducted using Stata version 14.0, with a significance level of 5%accepted. Monetary values were expressed in nominal 2019 reais.

III. RESULTS

Of 207,845 people aged 18 and older in the 2019-PNS registry, 30% were competent and remained in the analysis. Of this group, 22.7% required healthcare in the last two weeks. Fifty per cent of the demand was for public services, while 32% was for private services.

The main reasons for healthcare demand were illness or disease control (46%), medical check-ups (17%), diagnostic exams (13%), dental problems (6%), and other health-related services (6%). Only 3.7% of those who sought healthcare were not attended to.

During the two weeks preceding the completion of the questionnaire, 14,181 adults required healthcare services. This group had an average age of 51.4 and primarily consisted of women living in urban areas. The monthly household income for individuals in the first and tenth deciles was R$521 and R$ 18,355, respectively. Those in the wealthiest 10% had 35 times more income than those in the poorest 10%. There was a clear correlation between income and the likelihood of having private health or dental insurance.

Table 1 presents the geographic, socio-demographics, and health characteristics of the sample. Of those requiring healthcare services, 48% rated their health as “good/very good”, while 13% reported “bad/very bad” health”. Chronic diseases were present in 76% of patients, and sleep disturbance was reported by 52%. A significant portion of patients were moderate or excessive drinkers (33%), current smokers (11%), physically inactive (13%), had sedentary behaviour (12%), and used alternative medicine (11%). Additionally, 68% of patients participated in social activities in the last year. [Table 1 near here].

3.1 Propensity Score Model Performance

The multicollinearity diagnostic indicated no issues with multicollinearity. The propensity score was utilised for covariate adjustment to match participants seeking healthcare services with comparison groups that had similar background characteristics. The Hosmer-Lemeshow test showed a good fit for the propensity score model, and including the weighted propensity score in the propensity score

diagnostic model improved the balance of some baseline covariates. Table 2 presents the adjusted odds ratios for the final model of healthcare demand, which includes the product of the sampling weight and the propensity score weight. [Table 2 near here].

3.2 *Predicted Healthcare Demand Probabilities and Socioeconomic Inequalities.*

According to the final model, the probability that the adult Brazilian population would require healthcare within two weeks before the survey was 22.1%. An increasing gradient was observed from the poorest to the wealthiest deciles, with the wealthiest group having a 40% higher demand than the poorest. Those who sought healthcare services were three times more likely to demand them compared to those who did not.

Table 3 presents healthcare demand probabilities for relevant covariates related to health inequalities in the Brazilian adult population. Women have a significantly higher demand for healthcare than men across all income deciles, with the difference being more significant in the first five deciles. Wealthy individuals and those with higher incomes show significantly higher healthcare demand than the poorest, with this disparity being more pronounced in the most extreme deciles. Healthcare demand increases with age, with persons aged 60 or older demanding significantly more healthcare than their younger counterparts. Except for the older age group, the wealthiest tended to demand significantly more healthcare than their poorer counterparts in the remaining age groups. [Table 3 near here].

Higher levels of education lead to an increased demand for healthcare, with Brazilian adult graduates showing the highest demand. Wealthy individuals across all education levels are more likely to demand healthcare than the poor. These differences are statistically significant throughout all deciles.

Individuals with health insurance require significantly more healthcare than those without across all income deciles. In the poorer five deciles, those with health insurance have a declining higher probability of requiring healthcare than the general population, while individuals without health insurance follow a similar demand pattern to the general population.

The wealthier Wealthier five deciles have a slightly steady increase and decrease in healthcare demand with and without health insurance. No significant difference in demand probability exists between the poorest and wealthiest individuals without health insurance.

In the sample, doctors' rates were higher in capital areas than in interior municipalities, resulting in higher healthcare demand. However, when doctors' rates were below the median, capital areas showed lower healthcare demand than interior municipalities. Conversely, except for the first two deciles, when doctors' rates were above the median, interior municipalities had higher healthcare demand than capital areas. Wealthier individuals were significantly more likely to demand healthcare in both areas when doctors' rates were above the median, but only in interior municipalities when below the median.

Healthcare demand increases inversely with self-rated health. Individuals with “bad/very bad” SRH have significantly higher healthcare demand than those with fair and “good/very good’ SRH. However, those with “good/very good” SRH have a lower likelihood of healthcare demand than the average population, particularly in the lower income deciles. Wealthier individuals are significantly more likely to seek healthcare across all categories of self-rated health (SRH).

Individuals with three or more chronic diseases required significantly more healthcare than those with 1 or -2, or no chronic diseases. Wealthier individuals, regardless of the number of chronic diseases, have a higher demand for healthcare than poorer individuals. While the number of chronic diseases is higher, the gap in healthcare demand between the most affluent and poorer individuals is less pronounced.

Individuals with sleep disturbances, regardless of their income level, tend to require more healthcare. Those experiencing severe sleep disturbances demand significantly more

healthcare than those with moderate or no disturbances.

Wealthier individuals with severe sleep disturbances have a significantly higher demand for healthcare than the poorest, but this difference decreases as the severity of the disturbance increases.

IV. DISCUSSION

Over the last few decades, numerous studies have analysed the correlation between income inequality and healthcare access and utilisation from a supply-side perspective. However, it is still Critical to comprehend the connection between income inequality and healthcare from a demand-side perspective.

The paper analyses healthcare demand probability in Brazil's adult population based on sociodemographic and health factors, with a focus on household income differences. The study uses a propensity score to adjust for confounding variables and a balanced sample to build a healthcare demand model. Validity is enhanced by incorporating sampling weights and a weighted propensity score, resulting in more precise and generalisable outcomes (Dugoff et al., 2014; Guo et al., 2020).

Our findings indicate a clear trend in healthcare demand, showing that the probability of seeking healthcare increases significantly from the poorest to the wealthiest income deciles. the wealthiest adult Brazilians had a 40% higher likelihood of seeking healthcare compared to those in the poorest income bracket. This result is surprising, as one might expect that lower income would correlate with higher health needs and consequently greater demand for healthcare services.

According to the Aday-Andersen behavioural framework, our findings suggest that income inequalities are strongly associated with the predisposing, enabling, and need factors in determining an individual's likelihood of healthcare demand. The probability of healthcare demand increases from the poorest to the wealthiest deciles, as observed in predisposing factors such as sex, age, and education level. Furthermore, wealthier individuals consistently experience more favourable healthcare outcomes than the poorest ones.

For the enabling factors, the poorest individuals without health insurance were slightly more likely to demand healthcare than the wealthiest; however, this difference was not statistically significant. Conversely, we found that the poorest individuals with health insurance displayed significantly higher probabilities of seeking healthcare than the most affluent individuals, suggesting that the moral hazard associated with having private health insurance may lead to increased demand from private healthcare who had health insurance displayed significantly higher probabilities of seeking healthcare than the most affluent individuals, suggesting that the moral hazard associated with having private health insurance may lead to increased demand from private healthcare providers.

Additionally, our findings align with numerous empirical studies that highlight a close association between healthcare demand and the density of doctors in a specific area (Dzampe & Takahashi, 2022; Sekimoto & Ii, 2015; Tsai et al., 2004; Xirasagar & Lin, 2006). Even when the doctor's rate was highly concentrated in capital areas, individuals in interior municipalities still had a higher demand for healthcare, suggesting that other factors, such as income and health insurance, equalise the doctor's rate effect on healthcare demand.

Regarding the need factors, we found that self-rated health, the number of chronic diseases, and sleep disturbances are strong predictors of the probability of healthcare demand. Furthermore, in all categories of these factors, an increasing healthcare demand gradient across income deciles suggests that income distribution has a significant influence on healthcare demand.

In our study, healthcare demand corresponds to an event preceding access or utilisation of health services, making it challenging to compare our findings with empirical evidence on income disparities associated with healthcare access or

utilisation. However, it is possible to compare factors associated with income and sociodemographic disparities. Our findings suggest that even when predisposing, enabling and need factors are relevant in determining healthcare demand, income disparities strongly equalise this relationship. These findings differ from studies that have shown a negative relationship between low-income and vulnerable groups and healthcare access (Malta et al., 2021; Ogundipe & Adesola, 2022; Tzogiou et al., 2021; Zhang et al., 2015).

A significant strength of this study is its large, representative sample, which accounts for various significant economic and sociodemo- graphic factors. A propensity score- weighted approach was employed to minimise potential selection bias, enhancing both internal and external validity and allowing the results to be more generalisable. However, the study has several limitations: 1) the data relied on self-reported information, which could lead to subjective biased perception about their health conditions, affecting their decision to require healthcare, 2) the data was collected based on a two-week recall, which may not account for seasonal variation in acute diseases, 3) the analysis was based on cross-sectional data, which means causal relationships cannot be inferred. 4) The analysis did not account for other factors that influence healthcare demand, such as health literacy, self-care practices, distance to healthcare facilities, and waiting times. Therefore, caution is advised when interpreting the study findings.

These unobserved factors could introduce endogeneity and potential confounding effects.

The Brazilian healthcare system provides free and equal healthcare access, but there is still a gap in healthcare demand. Regardless of the enabling, predisposing, and need factors, wealthier socioeconomic groups are more likely to seek healthcare than vulnerable populations. Understanding healthcare demand in Brazil can help inform the development of effective policies and allocate resources to address healthcare inequalities.

Future research should focus on personality traits and individual behaviour, and consider the impact of private health insurance on healthcare demand and expenditures. Monitoring the effect of private health insurance is Critical to ensure supplier interests do not influence healthcare services.

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Table 1: Participants'Participants Characteristics According to Healthcare Demand Categories

Characteristics	Healthcare demand procure healthcare (n:14,181)	 no procure healthcare (n:48,273)
Avg. Age , years (Std.) **	51.4 (16.50)	47.7 (16.65)
**Age groups **		
18-39 (ref.)	3,891 (27.4%)	17,697 (36.7%)
40-59	5,432 (38.3%)	17,699 (36.7%)
60 or over	4,858 (34.3%)	12,877 (26.7%)
sex (n, women) **	9,601 (67.7%)	26,880 (55.7%)
marital status (n, married) **(n.s.)**	5,555 (39.2%)	18,592 (38.5%)
urban residence (n) **	11,645 (82.1%)	36,136 (74.9%)
working (n) **n.s.**	7,238 (51.0%)	28,535 (59.1)%
health insurance (n) **	4,318 (30.4%)	9,993 (20.7%)
dental health insurance (n) **	2,110 (14.9%)	5,284 (10.9%)
**education level **		
Elementary School	6,786 (47.9%)	23,637 (49.0%)
High School	4,048 (28.5%)	15,470 (32.0%)
Graduate school (ref.)	3,347 (23.6%)	9,166 (19.0%)
household income decils (n) **		
1st decile	1,369 (9.7%)	5,626 (11.7%)
2nd decile	2,201 (15.5%)	7,661 (15.9%)
3rd decile	1,253 (8.8%)	4,690 (9.7%)
4th decile	1,728 (12.2%)	6,208 (12.9%)
5th decile	1,246 (8.8%)	4,400 (9.1%)
6th decile	1,167 (8.2%)	4,060 (8.4%)
7th decile	1,169 (8.2%)	4,114 (8.5%)
8th decile	1,259 (8.9%)	3,985 (8.3%)
9th decile	1,308 (9.2%)	3,736 (7.7%)
10th decile	1,481 (10.4%)	3,793 (7.9%)
**region **		
north	2,209 (15.6%)	9,620 (19.9%)
northeast	4,662 (32.9%)	16,831 (34.9%)
central west	1,590 (11.2%)	5,627 (11.7%)
southeast	3,640 (25.7%)	10,040 (20.8%)
south (ref.)	2,080 (14.7%)	6,155 (12.8%)
**self-rated health status **		
bad(bad/very bad)	1,886 (13.3%)	2,620 (5.4%)
fair	5,521 (38.9%)	14,289 (29.6%)
good(good/very good)(ref.)	6,774 (47.8%)	31,364 (65.0%)
**number chronic diseases **		
none (ref.)	3,369 (23.8%)	22,592 (46.8%)
1-2	6,566 (46.3%)	19,380 (40.1%)
3+	4,276 (30.2%)	6,301 (13.1%)
smoking (n) **	1,533 (10.8%)	6,442 (13.3%)
**drinking alcohol **		
never drink(ref.)	9,420 (66.4%)	29,405 (60.9%)
moderate	1,576 (11.1%)	5,952 (12.3%)
excessive	3,185 (22.5%)	12,916 (26.8%)

Table 2: Estimated Odds Ratio, Standard Error and 95% ConfidenceConfidences Intervals for Healthcare Demand Logistic Regression Model (n: 16,284)

	Odds Ratio	Std. Err.	95% Conf. Interval	p-value
Age groups				
40-59 y-old	1.203	0.0607	(1.090 - 1.328)	0.000
60+ y-old	1.536	0.1259	(1.309 - 1.804)	0.000
Women	1.601	0.0768	(1.458 - 1.759)	0.000
Married	0.775	0.0384	(0.703 - 0.854)	0.000
Working	1.136	0.1098	(0.941 - 1.374)	0.185
Urban residence	0.713	0.0549	(0.613 - 0.829)	0.000
Education level				
high School	0.704	0.0411	(0.628 - 0.789)	0.000
elementary School	0.645	0.0481	(0.557 - 0.747)	0.000
Household income deciles	0.946	0.0098	(0.927 - 0.966)	0.000
Region				
north	2.435	0.2135	(2.050 - 2.892)	0.000
northeast	1.650	0.1250	(1.423 - 1.915)	0.000
central west	1.728	0.1449	(1.466 - 2.037)	0.000
southeast	0.482	0.0379	(0.413 - 0.562)	0.000
Health insurance	1.645	0.1021	(1.457 - 1.859)	0.000
Dental health insurance	1.264	0.0760	(1.124 - 1.422)	0.000
Self-rated health status				
fair	1.800	0.1024	(1.610 - 2.012)	0.000
bad	2.910	0.3862	(2.244 - 3.775)	0.000
Number chronic diseases				
'1-2	2.174	0.1121	(1.965 - 2.405)	0.000
3+	2.964	0.2264	(2.552 - 3.443)	0.000
Drinking alcohol				
moderate	0.930	0.0620	(0.816 - 1.060)	0.278
excessive	0.917	0.0485	(0.827 - 1.017)	0.101
Smoking	0.975	0.0780	(0.834 - 1.140)	0.756
Physical activity				
recommended	0.870	0.0498	(0.778 - 0.974)	0.015
inactive	0.920	0.5640	(0.816 - 1.037)	0.173
Sedentary lifestyle				
moderate time	0.947	0.0666	(0.825 - 1.087)	0.438
many time	0.911	0.0866	(0.756 - 1.098)	0.327
Sleep disturbances				
moderate	1.420	0.0747	(1.281 - 1.574)	0.000
severe	1.980	0.1355	(1.730 - 2.263)	0.000
Alternative medicine	1.394	0.0940	(1.221 - 1.591)	0.000
Doctors rate	1.175	0.0108	(1.154 - 1.196)	0.000
Social participation	1.228	0.0812	1.078 - 1.398)	0.002
Sample weigth*P. Score weig	1.461	0.0148	(1.432 - 1.490)	0.000

Table 3: Predicted Healthcare Demand Probabilities by Socio-Demographics, and Health Factors and Income Disparities

(deciles)	I	II	III	IV	V	VI
Population	0,197	0,175	0,201	0,192	0,201	0,210
Sex						
Men	0,127	0,129	0,140	0,141	0,132	0,153
Women	0,258	0,228	0,260	0,247	0,275	0,272
Age groups						
18-39 y-old	0,156	0,154	0,168	0,159	0,175	0,185
40-59 y-old	0,246	0,203	0,236	0,226	0,223	0,235
60 or more years	0,262	0,220	0,295	0,274	0,262	0,239
Education level						
elementary	0,194	0,171	0,200	0,202	0,214	0,218
high	0,184	0,165	0,188	0,177	0,183	0,177
graduate	0,281	0,221	0,246	0,213	0,223	0,260
Health insurance						
without	0,193	0,166	0,195	0,181	0,195	0,184
with	0,347	0,276	0,253	0,254	0,230	0,285
State areas doctors' rate						
IM States-under	0,176	0,156	0,187	0,181	0,190	0,191
IM States-upper	0,213	0,177	0,248	0,216	0,226	0,273
CS States-under	0,185	0,143	0,132	0,157	0,167	0,144
CS States-upper	0,270	0,211	0,223	0,204	0,211	0,217
Self-rated health status						
very good/good	0,141	0,129	0,151	0,150	0,159	0,178
fair	0,260	0,265	0,295	0,289	0,296	0,305
bad/very bad	0,456	0,399	0,427	0,474	0,466	0,456
Number of chronic diseases						
none	0,117	0,111	0,115	0,117	0,131	0,136
1-2	0,256	0,239	0,264	0,258	0,255	0,268
3+	0,388	0,393	0,411	0,376	0,411	0,404
Sleep Disturbances						
no day	0,144	0,137	0,153	0,148	0,161	0,172
moderate	0,256	0,235	0,270	0,240	0,245	0,248
severe	0,358	0,280	0,365	0,361	0,358	0,366

IM: Interior Municipalities of the States; **CS**: Capital of the States; **Under**: under the median (2.03): **Upper:** u

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ABSTRACT

Chronic pain has become an increasingly prevalent condition in today's world, and the use of opioids remains one of the main strategies for managing this type of pain. In this context, the search for predictive biomarkers of opioid dependence in patients with chronic pain represents an urgent clinical need, given the growing use of these drugs and the risks associated with long-term treatment. Although several advances have been made in the field of pain neurobiology, the literature remains scarce and heterogeneous, requiring a multidisciplinary and systematic approach to consolidate current evidence and outline new investigative pathways.

Keywords: biomarkers, chronic pain, opioid, opioid use disorder, neural alterations.

Classification: NLM Code: QZ 50

Language: English

LJP Copyright ID: 392842

Great Britain Journals Press

London Journal of Medical & Health Research

Volume 25 | Issue 6 | Compilation 1.0

Advances to Establish Biomarkers Predictive of Opioids use Disorder in Patients with Chronic Pain

Avanços no Estabelecimento de Marcadores Biológicos Preditivos da Dependência de Opióides em Pacientes com Dor Crônica

Giovanna Prudente Buccino[α], Gabrielle Brandão Vasconcelos[σ], Larissa Enes Cota[ρ], Reynaldo Yuji Souza Tanaka[ω], Vitor Hiraoka Fukamachi[¥], Ana Clara Brandão Guimarães[χ], Camila Sauberman Ribeiro[ν], Fernando Tarcsay Marques Neto[Θ] & Letícia Jabor Veiga[ζ]

RESUMO

A dor crônica vem se tornado uma condição cada vez mais prevalente no mundo atual e o uso de opióides ainda se mostra uma das principais alternativas para o controle desse tipo de dor. Nessa perspectiva, a busca por biomarcadores preditivos da dependência de opióides em pacientes com dor crônica representa uma necessidade clínica urgente diante do uso crescente desses fármacos e dos riscos associados ao tratamento prolongado. Embora diversos avanços tenham sido feitos no campo da neurobiologia da dor, a literatura ainda se mostra escassa e heterogênea, exigindo uma abordagem multidisciplinar e sistemática para consolidar as evidências atuais, bem como traçar novos caminhos de investigação. Trata-se de uma revisão bibliográfica que buscou nas bases de dados PubMed, Scielo e Cochrane, com os descritores "dor crônica", "biomarcadores", "alterações neurais" e "opióides". Dois autores avaliaram independentemente os títulos e resumos encontrados, seguido por seleção por texto completo por todos os autores. Os resultados evidenciam diferentes tipos de biomarcadores com potencial preditivo para transtorno de uso de opióides. Foram identificadas alterações na disponibilidade de receptores μ-opióides (MOR) no sistema nervoso central, especialmente em áreas como a amígdala e o núcleo accumbens, associadas ao maior risco de uso indevido. Evidenciaram-se também microRNAs específicos, como let-7, miR-103/107 e miR-146a, envolvidos na regulação negativa dos receptores MOR e na mediação de processos inflamatórios e neuroplásticos. Além disso, foram observadas variantes genéticas associadas à predisposição ao uso problemático de opióides, bem como biomarcadores imunológicos periféricos, como IL-6 e TNF-α, e metabólitos como o quinolinato.

A integração dessas descobertas sugere que múltiplos sistemas - genético, imunológico e neurofuncional - estão envolvidos na vulnerabilidade à dependência. A discussão dos achados aponta para a relevância clínica de integrar dados moleculares, genéticos, epigenéticos e neuroimagem no desenvolvimento de painéis biomarcadores aplicáveis ao acompanhamento de pacientes com dor crônica.

Ferramentas como RT-qPCR, citometria de fluxo e testes sensoriais quantitativos, associadas a algoritmos de aprendizado de máquina, surgem como estratégias promissoras para viabilizar uma abordagem personalizada, segura e eficaz no manejo da dor e prevenção da dependência. Conclusão: A incorporação de biomarcadores preditivos de dependência de opióides no painel clínico de pacientes com dor crônica é um caminho promissor para a vigilância do uso de opióides e para promoção de uma medicina individualizada. Os caminhos para seu estabelecimento devem permear o estudo dos biomarcadores. São necessários mais estudos, incluindo a população com dor crônica, para consolidar biomarcadores.

London Journal of Medical & Health Research

Palavras Chave: biomarcadores, dor crônica, opióide, transtorno do uso de opioides, alterações neuronais.

ABSTRACT

Chronic pain has become an increasingly prevalent condition in today's world, and the use of opioids remains one of the main strategies for managing this type of pain. In this context, the search for predictive biomarkers of opioid dependence in patients with chronic pain represents an urgent clinical need, given the growing use of these drugs and the risks associated with long-term treatment. Although several advances have been made in the field of pain neurobiology, the literature remains scarce and heterogeneous, requiring a multidisciplinary and systematic approach to consolidate current evidence and outline new investigative pathways. This is a literature review that searched the PubMed, SciELO, and Cochrane databases using the descriptors "chronic pain," "biomarkers,", "neuronal alterations" and "opioids." Article selection was performed first by title and then by full-text screening. Two authors independently evaluated the articles, followed by full-text selection by all authors. The results highlight different types of biomarkers with predictive potential for opioid use disorder. Alterations in the availability of μ-opioid receptors (MOR) in the central nervous system-particularly in regions such as the amygdala and nucleus accumbens-were identified and associated with a higher risk of misuse. Specific microRNAs, such as let-7, miR-103/107, and miR-146a, were also evidenced, being involved in the negative regulation of MOR and in the modulation of inflammatory and neuroplastic processes. Additionally, genetic variants associated with a predisposition to problematic opioid use were observed, as well as peripheral immunological biomarkers such as IL-6 and TNF-α, and metabolites like quinolinate. The integration of these findings suggests that multiple systems-genetic, immunological, and neurofunctional-are involved in vulnerability to dependence. The discussion of the findings emphasizes the clinical relevance of integrating molecular, genetic, epigenetic, and neuroimaging data in the development of biomarker panels applicable to the monitoring of patients with chronic pain. Tools such as RT-qPCR, flow cytometry, and quantitative sensory testing, combined with machine learning algorithms, emerge as promising strategies to enable a personalized, safe, and effective approach to pain management and dependence prevention. Conclusion: The incorporation of predictive biomarkers of opioid dependence into the clinical evaluation of patients with chronic pain is a promising path for monitoring opioid use and promoting personalized medicine. The path to their implementation must involve extensive study of these biomarkers. Further research, including studies involving chronic pain populations, is needed to consolidate the clinical applicability of these biomarkers.

Keywords: biomarkers, chronic pain, opioid, opioid use disorder, neural alterations.

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I. INTRODUÇÃO

Mundialmente, a dor é a principal causa de incapacidade, e sua persistência, transpassando o período normal de recuperação caracteriza a dor crônica, quadro álgico persistente e multifatorial mesmo após a resolução da lesão ou evento desencadeante, que demanda altos custos financeiros, para o sistema de saúde e para os pacientes [1]. Nos Estados Unidos (EUA) a dor crônica é caracterizado por um dos problemas de maior recorrência de atendimentos ambulatoriais, acometendo um equivalente de mais de um quarto da população do país e tendo um gasto que ultrapassa 100 bilhões de dólares anuais em despesas de saúde relacionadas ao manuseio dessa dor e da contenção da dependência em opióides, isso é, uma despesa que supera o financiamento combinado no tratamento de câncer, diabetes e doenças cardíacas [2].

Entretanto, observa-se imensa insatisfação com as intervenções terapêuticas, majoritariamente ineficientes em ação e aderência, entrelaçada ao conhecimento neurobiológico restringido sobre

mecanismos etiológicos associados à cronicidade álgica, e consequentemente, os mecanismos farmacológicos associados à analgesia persistente casos crônicos. [1; 3]. Outrossim, a subjetividade inerente aos processos álgicos, incluindo a mensuração e o prognóstico, agregada aos potenciais efeitos colaterais, utilização inadequada e dependência iminente dos medicamentos prejudicam intervenções terapêuticas farmacológicas atuais [3]. O desenvolvimento concomitante de dependência medicamentosa, principalmente em relação ao uso de opióides, apresenta significativa prevalência, conforme evidências recentes da National Institutes of Health (NIH) e da Federal Drug Administration (FDA). Este fenômeno está associado à incapacidade progressiva, e à sobrecarga nos custos de saúde, particularmente devido ao aumento das notificações de óbito pelo uso indiscriminado destes grupamento farmacológico. [4]

A dependência medicamentosa refere-se ao uso crônico de fármacos, especialmente em pacientes com dor crônica, e ocorre mais frequentemente pelo consumo de opióides, caracterizando o transtorno do uso de opióides (TUS). Esse transtorno se manifesta por um desejo intenso de consumir opióides, aumento da tolerância a esse grupo farmacológico e sintomas de abstinência em casos de descontinuidade do uso. O TUS afeta aproximadamente 16 milhões de pessoas, sendo mais de 2,1 milhões nos Estados Unidos, com mais de 120.000 mortes anuais atribuídas ao uso de opióides, entre os quais compreende-se a morfina, a codeína e a oxicodona. Estes fármacos são reconhecidos como terapias legítimas para pacientes com dor crônica severa não relacionada ao câncer e refratária ao tratamento com outras terapias conservadoras. De acordo com o DSM-5, o diagnóstico de TUS requer que o indivíduo tenha feito uso repetido de opióides nos últimos 12 meses, levando a sofrimento, desconforto e estresse com dois ou mais dos fatores comportamentais especificados, a presença de mais de seis desses critérios confirma a forma severa do transtorno [5].

Observa-se que alguns polimorfismos genéticos podem contribuir para as variações individuais no consumo de morfina. Por exemplo, o polimorfismo de um nucleotídeo único no gene do receptor Mu opióide 1 (OPRM1) e o polimorfismo G472A no gene da COMT (catecol-O-metiltransferase) estão relacionados à sensibilidade à dor, analgesia e ao potencial de dependência de opióides, e à percepção da dor, respectivamente. Além desses, o polimorfismo de 10 nucleotídeos únicos e a variação no número de cópias (CNV) do gene CYP2D6, associado ao metabolismo de fármacos e à resposta dos pacientes a esses medicamentos [5].

Na dor crônica há evidências crescentes que mostram haver uma reorganização ampla no cérebro, com alterações metabólicas cerebrais em regiões da dor, reestruturações da substância cinza em diferentes variações de dor crônica, sejam essas locais ou na estruturação de inter-relação do neocórtex, tendo em vista a temporalidade e a persistência da dor. Nesse sentido, os biomarcadores não podem ser generalizados e sim estudados para cada tipo específico de dor crônica, potencialmente podendo ter função de diagnóstico, prognóstico, preditivos e farmacodinâmicos, além de permitir a análise quanto a sua relação com a dependência medicamentosa. Entretanto, ainda existem conflitos científicos quanto a relação e padrões compartilhados nas diferentes condições álgicas progressivas existentes [4].

Nesse sentido, tendo em vista a gravidade e importância desse tema, esse artigo tem o objetivo de conduzir uma revisão bibliográfica para identificar e analisar os marcadores biológicos preditivos de dependência medicamentosa em pacientes com dor crônica. Através da análise de estudos recentes, visando entender a influência desses biomarcadores e sua relevância na identificação de dependência em pacientes com dor crônica, visando uma melhor conduta e intervenção precoce.

II. MÉTODOS

O presente trabalho trata-se de uma revisão bibliográfica realizada em 2025, que teve como objetivo identificar e analisar os potenciais biomarcadores preditores de dependência de

opióides em pacientes com dor crônica. Buscou-se nas bases de dados PubMed, SciELO e Cochrane, utilizando os descritores: “dor crônica”, “biomarcadores”, “alterações neurais” e “opióides”, artigos publicados nos últimos 5 anos, sendo incluídos apenas artigos com texto completo disponível publicamente em inglês, português ou espanhol.

Foram encontrados 73 artigos, na busca inicial, dos quais 18 foram selecionados para segunda avaliação e 5 para a revisão propriamente dita. A condução da pesquisa iniciou-se pela definição dos descritores. A triagem foi realizada em duas etapas. Primeiramente, dois autores analisaram independentemente os títulos e resumos com base nos critérios de inclusão: estudos originais, avaliação de biomarcadores com potencial preditivo de dependência ou uso problemático de opioides e população composta por pacientes adultos com dor crônica não oncológica. Também foram incluídos estudos em populações com uso inadequado de opioides e modelos animais que apresentassem potencial para estudo clínico. Foram excluídos relatos de caso e pesquisas cujo foco não envolvia diretamente ou indiretamente a relação entre biomarcadores e dependência de opióides.

Em seguida, os 18 artigos resultantes da primeira avaliação passaram por uma seleção por texto completo. Nessa etapa, todos os autores participaram da leitura integral dos textos de forma independente. Ao final, cinco estudos atenderam integralmente aos critérios de inclusão e foram selecionados para compor a presente revisão.

Os dados extraídos dos estudos incluíram: autores, ano de publicação, tipo de estudo, características da população avaliada, biomarcadores analisados, métodos de detecção dos biomarcadores e principais achados relacionados à predição de dependência de opióides. Caso houvesse divergência na seleção dos estudos, os autores responsáveis deveriam entrar em consenso.

Todos os dados utilizados foram extraídos de fontes secundárias de domínio público, não sendo, portanto, necessária a submissão do projeto a um Comitê de Ética.

III. RESULTADOS

A tabela 1 apresenta os resultados encontrados na revisão, organizados com base no nome dos autores e ano do estudo, objetivo, metodologia, biomarcadores avaliados e a associação entre esses marcadores e seu potencial uso para avaliar o risco de desenvolver um transtorno do uso de opióides por pacientes com dor crônica.

Tabela 1: Estudos Incluídos Sobre Biomarcadores Preditores De Dependência De Opióides Em Dor Crônica

Autores (Ano)	Objetivo do Estudo	Metodologia	Biomarcadores Avaliados	Principais Resultados e Conclusões
Ballester et al. (2022)[6]	Avaliar a relação entre função do sistema pióide endógeno e risco de uso indevido de opioides em dor lombar crônica	Estudo clínico com PET scan utilizando [11C]- carfentanil em 28 pacientes com dor lombar crônica e 15 controles; subdivisão dos pacientes em grupos de alto e baixo risco de uso indevido com base no Pain Medication Questionnaire (PMQ).	Disponibilidade de receptores μ-opióides (MOR) no cérebro.	Maior MOR basal na amígdala e menor ativação no núcleo accumbens em pacientes de alto risco.
Davis et al. (2020) [10]	Estabelecer diretrizes para validação de biomarcadores no contexto de dor e risco de dependência de opióides	Consenso técnico da NIH HEAL Initiative envolvendo pesquisa-dores, reguladores e clínicos. Discutiu critérios e prioridades para validação de bio marcadores aplicáveis à dor e ao risco de dependência de opióides.	Biomarcadores ômicos (genômica, transcriptômi ca, proteômica), neuroimagem (MRI, PET), eletrofisiologia (EEG), testes sensoriais (QST) e modelos compostos.	Destacou a necessidade de validação rigorosa, repro-dutibilidade e integração de biomarca dores em múltiplas plataformas para uso clínico. Proposta de frameworks para acelerar a tradução dos achados em aplicações terapêuticas personalizadas.
Deng & Zou (2023) [9]	Investigar o papel de RNAs não codificantes na tolerância e dependência a opióides em modelos animais	Revisão sistemática de evidências experimen-tais em modelos animais de tolerância a opióides, com foco em mecanismos moleculares mediados por RNAs não codificantes. Ausência de dados clínicos humanos limita a aplicabilidade direta dos achados.	MicroRNAs (let-7, miR- 103/ 107, miR- 378- 3p, miR-146a), longos ncRN As (lnc RNAs), RNAs circulares (circRNAs).	ncRNAs estão envolvidos na regulação da expressão do receptor MOR, vias inflamatórias e plasticidade sináptica. Evidências sugerem papel relevante na indução de tolerância e como alvos para prevenir ou reverter a dependência, embora a translação clínica ainda dependa de validações em humanos.
Malafoglia et al. (2022) [7]	Explorar a interação entre dor crônica, opioides e sistema imune com foco em possíveis biomarcadores	Revisão narrativa integrativa.	Biomarcadores periféricos e centrais, tais como: expressão de receptores opióides em células imunes (ex.: MOR em linfócitos – “Mu-Lympho-Mar ker”), microRNAs, citocinas (por exemplo, IL-6 e TNF-α) e metabólitos (ex.: quinolinato, ácido xanturênico).	Os achados sugerem a existência de múltiplos biomarcadores promissores para a predição do risco de dependência de opióides. Ressalta-se a importância da modulação da resposta imune e neuroinflamação na patogênese da dor crônica e na predisposição ao uso problemático de opióides.

Sanchez-Roige et al. (2021) [8]	Identificar variantes genéticas associadas ao uso problemático de opioides na população geral	GWAS com 132.113 participantes da 23 and Me. Embora a amostra inclua usuários de opióides em geral, o estudo não identificou especificamente um subgrupo com dor crônica.	Variantes genéticas (SNPs), com destaque para os loci rs3791033 (próximo a KDM4A/ PTPRF) e rs640561 (próximo de LRRIQ3).	Variantes associadas ao uso problemático de opióides, indicando predisposição genética. Aplicabilidade a pacientes com dor crônica deve ser interpretada com cautela devido à ausência de análise estratificada.

Os artigos analisados configuram uma complementaridade entre biomarcadores centrais (neuroimagem e genética) e periféricos (citocinas inflamatórias, miRNAs), destacando o papel dos mecanismos inflamatórios e epigenéticos na modulação da resposta aos opioides e no risco de dependência. Ademais a urgência de frameworks metodológicos validados para guiar a implementação clínica desses biomarcadores, também é abordada. Além disso, o desenvolvimento de algoritmos preditivos, baseados em aprendizado de máquina e alimentados por dados multimodais, é uma via promissora para integrar esses domínios.

IV. DISCUSSÃO

A dor crônica é uma condição complexa e multifatorial, em que há persistência da dor além do tempo esperado de recuperação, caracterizada por alterações profundas nas vias nociceptivas periféricas e centrais, como o aumento da excitabilidade de nociceptores e amplificação da transmissão sináptica na medula espinhal e no córtex, corroborando para uma desregulação do portal da dor. Além disso, há evidências da participação de processos inflamatórios sistêmicos, disfunções neuroendócrinas, alterações cognitivas e emocionais, como ansiedade e depressão, que interagem com o sistema opióide endógeno. Essa complexa rede de processos neurobiológicos contribui para a manutenção da dor, e para a modulação da resposta a opioides, que ainda se apresentam como uma importante intervenção terapêutica para esse quadro, colaborando com o risco de desenvolver dependência. [7]

Por mais que seus mecanismos não sejam devidamente esclarecidos, a dependência física de opióides é vastamente reconhecida na bibliografia. Esse fenômeno decorre de um fenômeno neurobiológico que engloba modificações em sistemas centrais de recompensa, vias de dor, circuitos de controle emocional e respostas imunes. Inicialmente, os opióides ativam receptores μ-opióides (MOR) no sistema mesocorticolímbico, estimulando intensa secreção de dopamina no núcleo accumbens, gerando resposta eufórica e reforço positivo. Com o uso crônico, ocorrem ajustes, como dessensibilização e internalização dos receptores MOR, elevando a necessidade de doses crescentes para obter um efeito semelhante, caracterizando tolerância. Concomitantemente, o organismo desenvolve dependência física, demarcada por sintomatologia de abstinência quando o uso é cessado. [6] Além disso, fármacos opióides podem ocasionar hiperalgesia paradoxal,

intensificando a dor crônica, e ativar células imunes do sistema nervoso central, como a microglia, secretando citocinas inflamatórias que prolongam a sensibilização neural. [7] Simultaneamente, componentes genéticos e epigenéticos, como polimorfismos em genes associados à resposta dopaminérgica ou à expressão de MOR, e a ação de microRNAs que regulam vias inflamatórias e receptores opioides, modulam a predisposição à dependência. [8,9,10] Esses processos interligados explicam o porquê de alguns indivíduos evoluírem negativamente da utilização terapêutica à utilização abusiva de opioides, e destacam a importância da identificação precoce de biomarcadores preditivos e da adoção de estratégias de medicina personalizada. Contudo, a identificação de marcadores biológicos para essa condição, associada ao tratamento do quadro álgico

persistente, ainda é uma lacuna na literatura atual.

A busca por biomarcadores preditivos de dependência de opióides em pacientes com dor crônica representa um dos maiores desafios da medicina translacional atual. A interferência de múltiplos fatores na dor crônica, somada ao risco de desenvolvimento de dependência, exige a integração de diversas abordagens biológicas, comportamentais e tecnológicas. Esta revisão buscou mostrar uma visão ampla dos principais avanços neste tema, abordando achados provenientes de estudos com diferentes metodologias, e abrangência em áreas da genética, epigenética, neuroimagem, imunologia e neurobiologia, a fim de oferecer um panorama dos caminhos viáveis para estabelecer e consolidar esses biomarcadores.

4.1 Interconexão Entre Os Sistemas Opióide, Imune E Nervoso Central

No contexto da presença de dor crônica, o transtorno de uso de opioides é o resultado de uma interligação entre os três sistemas: opióide, imune e nervoso. Estes podem ser alterados por fatores neuroinflamatórios, hormonais e comportamentais. Ao investigar integração destes, Malafoglia e col. (2022) [7] sustentam que a dor crônica pode produzir disfunções no nível do sistema imune, que se apresentam com níveis elevados de citocinas inflamatórias, como IL-6 e TNF-α, os quais modulam negativamente a resposta aos opióides. Ao analisar a porcentagem de células B expressando MOR, descobriu-se que ela é significativamente menor em pacientes com dor crônica, proporcional à gravidade do caso. Também é importante ressaltar que os participantes do estudo não estavam em uso de opioides, o que descarta a hipótese de dessensibilização farmacológica dos receptores. Com isso, essa expressão de MOR em linfócitos B poderia funcionar como biomarcador periférico de dor crônica, propondo o “Mu-Lympho-Marker” (MLM).

Em contrapartida, a exposição crônica aos opióides também parece comprometer o funcionamento do sistema imune, com um feedback que possivelmente contribui para a susceptibilidade à infecções e à dependência desses medicamentos. Adicionalmente, o eixo Hipotálamo-Hipófise-Adrenal (HHA) apresenta regulação cruzada com o sistema opióide e o sistema imune, na resposta ao estresse pelo organismo, o que leva o cortisol a ser reconhecido como biomarcador hormonal potencial.

As vias de recompensa no cérebro, particularmente o eixo córtex pré-frontal e sistema límbico, do qual o núcleo accumbens se apresenta como principal, foram moduladas pela dor e pelos opióides, dificultando distinguir entre a adaptação neuroplástica devido à dor e a adaptação relacionada à dependência. A superposição funcional embasa o princípio de aproximações integrativas, com múltiplos biomarcadores.

4.2 Receptores M-Opióides (Mor) Como Marcadores Funcionais

A expressão dos receptores μ-opióides (MOR) tem sido tópico de estudo com relevantes implicações clínicas. Tanto Malafoglia et al. como [7] Ballester et al. [6] consideram esses receptores como potenciais biomarcadores, porém em sítios diferentes. Enquanto o primeiro demonstra correlação com a superfície linfocitária e a resposta imune, o segundo se associa ao sistema nervoso central.

O estudo de Ballester et al. (2022) [6] demonstra, utilizando tomografia por emissão de pósitrons (PET) e o traçador [11C]-carfentanil, que pacientes com maior risco de uso indevido de opioides têm maior disponibilidade basal de MOR na amígdala, e maior desativação endógena na via do núcleo accumbens frente à dor. Os achados indicam uma perspectiva positiva do uso de medidas como "binding potential" e liberação de opióides endógenos em tempo real como marcadores preditivos. Contudo, a aplicabilidade destas medições é limitada por questões relacionadas ao alto custo e baixa acessibilidade. Dessa forma, novos estudos devem explorar formas menos invasivas e com mais aplicabilidade cotidiana do atendimento médico, buscando também a reprodutibilidade em amostras maiores

e devidamente estratificadas quanto aos subgrupos clínicos.

4.3 Variantes Genéticas Indicadoras De Predisposição

Sob uma perspectiva genética populacional, Sanchez-Roige et al. (2021) [8]realizaram um estudo de associação genômica ampla (GWAS) com mais de 130 mil participantes da plataforma 23andMe, com o objetivo de identificar variantes genéticas associadas ao uso problemático de opioides. Entre os principais achados, destacam-se os loci rs3791033 (próximo aos genes KDM4A e PTPRF) e rs640561 (localizado próximo ao gene LRRIQ3), ambos associados de forma significativa ao comportamento de uso não terapêutico de opioides. Esses resultados apontam para uma possível predisposição genética ao comportamento de risco, reforçando a existência de uma base hereditária na vulnerabilidade à dependência.

Apesar do grande tamanho amostral e da abordagem estatística ampliada, o estudo não incluiu análise estratificada para subgrupos clínicos, como pacientes com dor crônica. Isso limita a aplicabilidade direta dos achados a esse perfil específico de pacientes, que frequentemente fazem uso terapêutico de opioides. No entanto, a identificação de variantes com possível influência no comportamento aditivo oferece uma base relevante para estudos futuros com foco em dor crônica. A genotipagem de pacientes antes do início da terapia com opioides pode futuramente ajudar na estratificação de risco, auxiliando médicos na tomada de decisão quanto à escolha de terapias mais seguras ou à adoção de estratégias de monitoramento intensificado. A integração desses achados genômicos com outros biomarcadores (como neuroimagem, expressão de receptores e dados epigenéticos) poderá contribuir para a construção de modelos preditivos mais abrangentes e eficazes.

4.4 Micrornas Como Biomarcadores Moleculares Emergentes

Os microRNAs (miRNAs) são um grupo de RNAs não codificantes que chamaram a atenção como biomarcadores periféricos para a avaliação clínica da dependência de opióides. Em seus estudos, Deng e Zou (2023) [9] mostraram os miRNAs let-7, miR-103/107, miR-378-3p e miR-146a estão envolvidos na regulação negativa dos receptores MOR, processos inflamatórios e neuroplásticos, mecanismos centrais na adaptação ao uso crônico de opioides. Em particular, o miRNA let-7 tem sido associado à dessensibilização dos receptores MOR, reduzindo sua disponibilidade funcional, enquanto o miR-146a participa de mecanismos de feedback inflamatório que podem exacerbar a sensibilização centrallncRNAs e circRNAs também demonstram papel crucial na fisiopatologia da tolerância. Esses achados aprofundam os mecanismos epigenéticos específicos que, além de influenciarem a eficácia dos opioides, podem servir como biomarcadores moleculares da suscetibilidade à tolerância e à dependência.

Apesar da baixa padronização dos bancos de dados e a escassez de estudos em humanos, foi evidenciado que esses marcadores são estáveis no sangue, e detectáveis via RT-qPCR e microarrays, ressaltando seu potencial como possíveis biomarcadores. Além disso, os autores ressaltam que o uso experimental de inibidores de miRNAs, como os antagomiRs, mostrou potencial terapêutico ao restaurar a resposta aos opioides e reverter a tolerância em modelos animais. Tal observação reforça a hipótese, já discutida na revisão, de que a vulnerabilidade individual ao transtorno do uso de opióides, especialmente em contextos de dor crônica, pode estar fortemente vinculada à regulação epigenética de receptores e vias intracelulares associadas à analgesia. Nesse sentido, a incorporação dos ncRNAs ao painel de biomarcadores poderia não apenas permitir o diagnóstico precoce da dependência, mas também viabilizar abordagens mais precisas e personalizadas no tratamento com opioides, reduzindo os riscos de uso problemático.

No entanto, os próprios autores reconhecem uma limitação relevante: a maior parte dos achados foi obtida em modelos animais, sem validação clínica em populações humanas. Embora os efeitos dos ncRNAs sobre a resposta aos opioides sejam promissores, sua aplicabilidade em humanos -

particularmente em pacientes com dor crônica - ainda demanda confirmação por meio de estudos longitudinais, translacionais e estratificados. Essa limitação converge com uma das principais conclusões da presente revisão: a necessidade urgente de fortalecer a ponte entre os achados moleculares experimentais e a prática clínica.

Assim, os dados apresentados por Deng & Zou (2023) [9] não apenas sustentam, como expandem os argumentos discutidos na revisão, oferecendo uma base promissora para o desenvolvimento de biomarcadores moleculares epigenéticos e para a criação de intervenções terapêuticas mais eficazes e seguras no manejo da dor e da dependência a opióides. A exploração dos ncRNAs como alvos terapêuticos e preditores de risco representa um campo emergente que, com investimento contínuo em pesquisa translacional, pode revolucionar a abordagem clínica desses pacientes.

4.5 Superação A Subjetividade Da Dor E Comorbidades

A dor, embora tenha suas bases neurofisiológicas, também é um processo subjetivo, sendo frequentemente acompanhada de comorbidades psiquiátricas. Isso resulta em dificuldades à padronização dos biomarcadores, tendo em vista que cada indivíduo reage diferentemente à dor com base nas suas experiências e organismo.. Nesse sentido, intervenções que levem em conta esse aspecto da dor como Quantitative Sensory Testing (QST), análises multivariadas e a combinação de escalas clínicas e biomarcadores têm mostrado eficácia. Adicionalmente, as abordagens de modelagem estatística que incluem covariáveis, como dor, humor, uso de medicações e histórico de abuso, têm mostrado sucesso em sua utilização. [10]

4.6 Implicações Terapêuticas E Medicina Personalizada

A falta de diretrizes globais para a aplicação de opioides na terapia da dor crônica demonstra a importância da incorporação de biomarcadores no atendimento médico. Eles podem ser usados para determinar o medicamento e posologia ideais, acompanhar a resposta ao tratamento, detectar precocemente o uso abusivo ou inadequado dos medicamentos e ajudar na troca segura para outras intervenções terapêuticas. O uso de biomarcadores nos algoritmos clínicos representaria um avanço muito significativo em direção à medicina personalizada da dor, já que seria capaz de possibilitar intervenções mais adequadas, seguras e com melhores prognósticos.

No campo regulatório e metodológico, o estudo de Davis et al. (2020) [10] se destaca por contribuir de forma decisiva ao estabelecer um “framework” abrangente para a validação de biomarcadores no contexto da dor e do uso de opióides. Resultado de um consenso técnico entre especialistas, esse trabalho propõe critérios rigorosos para a seleção, mensuração e validação de biomarcadores, enfatizando a necessidade de estudos prospectivos, amostras bem caracterizadas, controle de variáveis confundidoras e reprodutibilidade interlaboratorial. Trata-se de uma perspectiva metodológica e regulatória essencial para o avanço da área, atuando como um marco norteador para a padronização da pesquisa translacional.

A proposta de um “framework” integrativo apresentada por Davis et al. [10] inclui abordagens multidimensionais, como plataformas ômicas (genômica, transcriptômica, proteômica), neuroimagem funcional (MRI, PET), eletrofisiologia (EEG), testes sensoriais quantitativos (QST) e dados clínicos estruturados. Essa convergência metodológica não apenas reforça a abordagem discutida ao longo da presente revisão, como também é considerada indispensável para o desenvolvimento de biomarcadores clinicamente acionáveis. Tais marcadores poderiam ter impacto direto na tomada de decisão terapêutica e na prevenção do uso indevido de opióides, especialmente em populações de risco.

Ademais, o estudo dialoga diretamente com os pontos centrais da presente revisão ao destacar a necessidade de reprodutibilidade interlaboratorial e o controle rigoroso de variáveis confundidoras, aspectos que representam barreiras significativas à consolidação de biomarcadores aplicáveis na

prática. Davis et al. [10] evidenciam que a heterogeneidade metodológica ainda presente na literatura limita a generalização dos achados e propõem a inclusão de múltiplos domínios biomédicos e comportamentais como estratégia para superar tais desafios. Essa abordagem se mostra especialmente pertinente diante da natureza complexa, multifatorial e subjetiva da dor crônica e sua sobreposição com o risco de dependência química.

Por fim, os autores reforçam a urgência da formação de consórcios multicêntricos e interinstitucionais como ferramenta estratégica para padronizar protocolos, ampliar o tamanho amostral e acelerar a translação clínica dos achados. Assim, o estudo de Davis et al. [10] atua como um guia estratégico para estruturar futuras investigações, integrando inovação tecnológica com rigor científico e oferecendo bases sólidas para a implementação dos biomarcadores preditivos no manejo da dor e da tolerância aos opióides.

4.7 Limitações E Perspectivas Futuras

Em virtude da escassez de estudos específicos realizados com a população de dor crônica, esta revisão agrupa dados obtidos em trabalhos ainda não aplicáveis a este grupo, mas passíveis de tradução. Estudos são necessários para avaliar diretamente a associação dos biomarcadores com a dependência de opióides nesta população. A formação de consórcios inter-institucionais e o desenvolvimento de protocolos padronizados são passos importantes para uma futura validação clínica.

V. CONCLUSÃO

A dependência de opióides em pacientes com dor crônica representa um dos desafios clínicos e científicos mais urgentes da medicina contemporânea. A presente revisão bibliográfica evidencia que o estabelecimento de biomarcadores preditivos para esse cenário não é apenas uma possibilidade teórica, mas uma necessidade estratégica para transformar o manejo da dor em um paradigma de medicina personalizada, segura e baseada em evidências.

Os estudos analisados revelam um panorama multifatorial no qual sistemas neurobiológicos, imunológicos, genéticos e epigenéticos interagem de maneira complexa na gênese da dor crônica e na suscetibilidade à dependência. Estudos reforçam a magnitude epidemiológica do problema e suas implicações clínicas e econômicas. Já outras pesquisas aprofundam a compreensão da dor como fenômeno neurofuncional mensurável, propondo biomarcadores intracranianos e contextuais com potencial diagnóstico.

No contexto da dependência, destacam-se os achados sobre a disfunção do sistema opióide endógeno que demonstram associações genéticas relevantes para a vulnerabilidade ao uso problemático de opióides. Alguns trabalhos acrescentam a esse panorama o papel da neuroinflamação, enquanto outros revelam o potencial dos RNAs não codificantes como alvos terapêuticos e preditivos. É proposto o rigor metodológico necessário para transformar descobertas biomoleculares em ferramentas clínicas acionáveis, sugerem uma abordagem integrativa e padronizada.

Assim, a construção de um painel multidimensional de biomarcadores - que inclua desde variantes genéticas e epigenéticas até sinais neurofuncionais e imunológicos -se configura como um caminho promissor para antecipar riscos, guiar intervenções terapêuticas e prevenir quadros de dependência. A superação das limitações atuais exige colaboração científica global, protocolos padronizados e vontade para priorizar essa agenda.

Portanto, esta revisão não apenas aponta caminhos viáveis para a identificação de marcadores biológicos preditivos, como também reafirma a urgência de uma nova era no tratamento da dor crônica: uma era em que o risco de dependência seja previsto, monitorado e evitado com base em ciência de ponta, garantindo ao paciente uma analgesia eficaz, segura e verdadeiramente personalizada. Logo, necessitam -se mais estudos sobre o assunto.

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"Targeted Therapies and their Associated Molecular Alterations in the Treatment of Renal Cell Carcinoma"

Priya Hays

INTRODUCTION

Renal cell carcinoma, (RCC) the most prevalent of kidney cancers, is a relatively common cancer, constituting approximately 10% of all cancers in adults. Many molecular subtypes have been characterized for RCC, the most common being clear cell RCC, or ccRCC, which occurs in close to 75% of cases, and has a strong association with mutations in the von Hippel-Lindau (VHL) tumor suppressor gene [1]. ccRCC constitutes close to 80% of metastatic presentations. Histology shows acinar growth and clear cell cytology, surrounded by a rich vasculature. Having a strong association with mutations in the von Hippel-Lindau tumor suppressor gene, ccRCC exhibits loss of VHL gene by 3p chromosomal loss at the 3p25 locus. Another histologic subtype includes non clear cell renal cell carcinoma nccRCC. Somatic ccRCC is characterized by inactivation of the protein products of VHL (pVHL), which promotes transcription of genes implicated in tumor formation and growth [1].

Keywords: NA

Classification: DDC Code: 616.99463

Language: English

Great Britain Journals Press

London Journal of Medical & Health Research

Volume 25 | Issue 6 | Compilation 1.0

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I. INTRODUCTION

Renal cell carcinoma, (RCC) the most prevalent of kidney cancers, is a relatively common cancer, constituting approximately 10% of all cancers in adults. Many molecular subtypes have been characterized for RCC, the most common being clear cell RCC, or ccRCC, which occurs in close to 75% of cases, and has a strong association with mutations in the von Hippel-Lindau (VHL) tumor suppressor gene [1]. ccRCC constitutes close to 80% of metastatic presentations. Histology shows acinar growth and clear cell cytology, surrounded by a rich vasculature. Having a strong association with mutations in the von Hippel-Lindau tumor suppressor gene, ccRCC exhibits loss of VHL gene by 3p chromosomal loss at the 3p25 locus. Another histologic subtype includes non clear cell renal cell carcinoma nccRCC. Somatic ccRCC is characterized by inactivation of the protein products of VHL (pVHL), which promotes transcription of genes implicated in tumor formation and growth [1].

Localized and systemic therapies differ on the basis of clinical presentation such as primary or metastatic disease, and they can be administered in first-line or adjuvant settings. Before the advent of precision medicine, renal cell carcinoma was treated with non-specific immunomodulatory agent such as cytokines [2]. IL-2 and high-dose interferon-alpha (HD IFN-alpha) were considered the treatment of choice for renal cell carcinoma due to the cancer's predisposition for lack of sensitivity to chemotherapy and hormonal therapy, however response was variable, with varying optimal effects and occurrence of toxicity. These treatments have been questioned due to data demonstrating that when these agents are administered in combination with VEGF targets, and they have shown less than ideal efficacy. Patients progressed on disease and were required to be followed up with systemic VEGFR targets in second line settings.

Prognostic factors associated with low-risk and high-risk RCC in terms of different staging systems also serve to determine appropriate therapies. Established staging systems most used in the traditional cytokine era were developed by a group at Memorial Sloan Kettering Cancer Center (MSKCC) [3]. MSKCC developed one of the most widely used prognostic systems which included parameters such as performance status less than 80%, >1.5 times the upper limit of normal of serum lactate dehydrogenase, with >10mg/dL of serum calcium, and decreased length of time for the initiation of systemic therapy after initial RCC diagnosis (<1 year) [3]. The staging system stratified patients in 3 risk categories based on the number of risk factors they possessed with poor risks having 3-5 factors, intermediate risks having 1-2 factors and no risk factors for favorable prognosis. Median overall survival (mOS) had corresponding values of 5, 14, 30 months [3].

For patients who were administered VEGFR targeted therapies (to be discussed later), the International mRCC Database Consortium (IMDC) developed a new model, which added 2 more prognostic factors: high absolute neutrophil and platelet count. According to Barata et al, "[i]n a population-based study with more than 1000 patients who received second-line targeted therapy for mRCC, the median OS was 35.3, 16.6, and 5.4 months for the favorable-risk, intermediate- risk, and poor-risk groups,

respectively [3].” The lower median OS in the poor-risk groups may indicate the prognostic factors of high absolute neutrophil and platelet count would indicate lack of clinical efficacy of the VEGFR inhibitor.

There is considerable debate surrounding the use of these targeted treatments for RCC. Systemic therapies for both localized and metastatic disease present with contradictory evidence in terms of conflicting median progression free survival (mPFS), median overall survival (mOS) and overall response rates (ORR). Vascular endothelial growth factor receptor (VEGFR) antiangiogenic agents were regarded as the mainstay for treating RCC, but recent evidence suggests that they may not be as effective. Mammalian target of rapamycin (mTOR) inhibitors demonstrated efficacy in a number of clinical trials, but controversy exists over their usage in clinical settings. Clinical trials for investigational compounds have emerged, including a new class of inhibitors called HIF inhibitors and a novel drug-antibody conjugate, but some have had relatively disappointing results. Immunotherapy agents, such as immune checkpoint inhibitors (ICIs), have made substantial inroads in the treatment of clear cell mRCC and have even entered into consideration as front line settings.

Since then, other second and third generation targeted therapies have emerged to overcome resistance of these first-generation agents, (tivozanlib, axitinib, cabozantinib and vorolanib) and combination approaches have been developed to ameliorate outcomes with more favorable toxicities. This paper serves as a review of novel targeted therapies for RCC, particularly localized and advanced ccRCC, and provides additional evidence for the clinical outcomes of these targeted therapies. [1,3,4].

1.1 VEGF/VEGFR/PDGFR (Platelet Derived Growth Factor Receptor) Targets

With discovery of the molecular alterations, such as the biallelic mutations inactivating the VHL tumor suppressor gene which leads to oncogenesis and ccRCC, targeted therapies such as bevacizumab, a VEFG-A targeted biologic, sunitinib, paxopanib and axitinib (the latter three being oral small molecule tyrosine kinase inhibitors that target VEGFR and PDGFR and have anti-angiogenic effects. (Figure 1) were studied in a series of clinical trials and proved to have robust clinical outcomes and favorable safety profiles that initiated a paradigm shift in the treatment of renal cell carcinoma from cytokines to targeted therapies [2]. VHL is implicated in the hypoxia-inducible pathway (HIP) which leads to overexpression of VEGFR and PDGFR, accounting for the clinical efficacy of these anti-angiogenic agents.

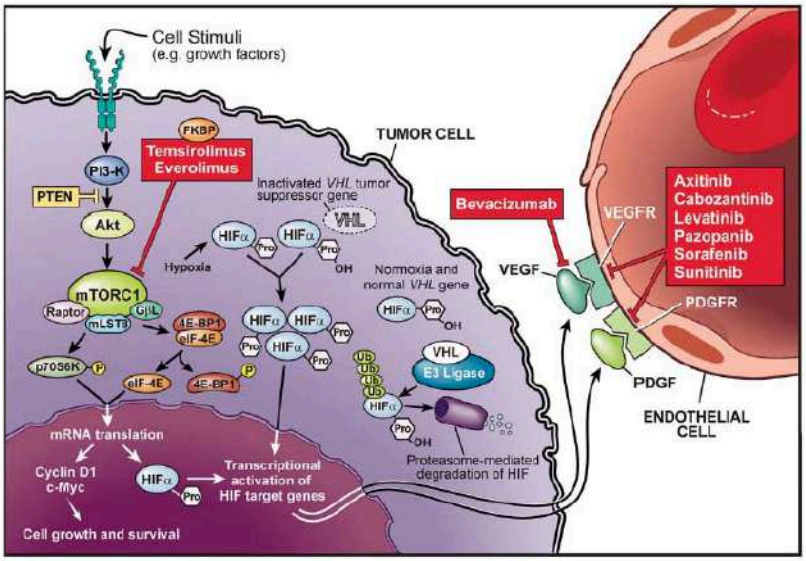

Figure 1: Cell Signalling Pathways Associated with Therapeutic Agents and their Targets for Ccrcc

Bevacizumab, a biologic targeting VEGF-A, was evaluated in randomized clinical trials and compared with IFN-alpha and placebo in front-line settings. In both trials, bevacizumab demonstrated superiority in PFS: more than twofold in PFS and a PR (partial response) greater than 2 years versus placebo; a mPFS of 10.2 months versus 5.4 months and response rate of 31% versus 13% with a medium duration of greater than 1 year when compared to IFN-alpha. Both trials elicited favorable safety profiles for bevacizumab which exhibited proteinuria and hypertension that lacked severity. Both results were confirmed in subsequent trials The success of bevacizumab could be due to strength in overcoming toxicities but maybe in a limited in overcoming intrinsic and acquired drug resistance.

Concomitantly, oral small molecule tyrosine kinase inhibitors (TKI) targeting VEGFR, such as sunitinib and sorafenib, were tested in clinical trials on untreated patients and both showed superiority over IFN-alpha in phase III trials. Sunitinib showed a mPFS of 11 months versus 5 months when compared IFN-alpha with a response rate of 31%. Sorafenib was compared to placebo in patients resistant to cytokine therapy and exhibited superiority over placebo with a mPFS of 5.5 months and 2.8 months, respectively.

Common adverse events (AEs) of greater than 20% consisted of fatigue and diarrhea, which were managed with dose reduction and changes to the dosing schedule. Another TKI, pazopanib displayed superiority over placebo and non-inferiority over sunitinib in phase III trials with better quality of life and less fatigue. Overall, antiangiogenic agents were implemented in first-lines settings and displaced generalized cytokine therapies. The clinical success of antiangiogenic targeted agents such as TKIs sunitinib and sorafenib with mPFS of 11 months and 5.5 months respectively versus placebo is associated with off-target effects however. (Mabeta) One review reported that "combining FGF/FGFR inhibitors with VEGF/VEGFR inhibitors are an excellent way to optimize the curative effect and expand the antitumour range because their combination can target both tumour cells and the tumour microenvironment." However, data for RCC was not reported.

Likewise, another target implicated in the HIF pathway was mTOR which led to the development of additional medications in the treatment of clear cell renal carcinoma. The mTOR pathway also leads to angiogenesis through its interaction with the HIF pathway. These mTOR inhibitors were shown in preclinical models to have antitumor activity, such as temsirolimus and everolimus for advanced ccRCC.

A treatment-naive patient population with poor risk was administered temsirolimus and compared with IFN-alpha and had mOS of 10.9 months versus 7.3 months. 20% of patients experienced side effects, which included rash, diarrhea, anemia, hyperglycemia. The RECORD-1 phase III study for late-stage ccRCC evaluated the oral mTOR inhibitor everolimus, was compared with placebo and was shown to have improved PFS of 4.0 months versus 1.9 months [2].

1.2 mTOR Inhibitors

A randomized phase 3 trial, RECORD-1, compared the efficacy of everolimus with placebo in 410 advanced RCC patients that had prior antiangiogenic therapy (sunitinib 46%; sorafenib 28%, both agents 26%) and were non-responsive. mPFS was 4 months and 1.9 months in the mTOR inhibitor arm and placebo respectively (HR, 0.30; 95% CI, 0.22-0.40). After updated analysis, mOS were 14.8 months and 14.4 months in the treatment arm and control group, respectively (HR, 0.87; P5.162). AEs were uncommon, with 13% of patients discontinuing treatment because of them. However, stomatitis, diarrhea and fatigue did occur [3].

In the treatment of renal cell carcinoma, anti-angiogenic tyrosine kinase inhibitors and mTOR inhibitors have emerged as efficacious treatments in the first-line settings, including bevacizumab, pazopanib, sunitinib, lenvatinib, which serve as potent VEGFR TKIs, and mTOR inhibitors everolimus, and temsirolimus [5]. Another trial evaluating sunitinib compared sunitinib to interferon-alpha and the data showed longer survival, with mPFS being 11 months for

sunitinib and 5 months with IFN-alpha with an hazard ratio of 0.42 (95% CI, 0.32-0.54; P < .001). [6] Another trial demonstrated pazopanib efficacy was similar to sunitinib demonstrating mPFS of 8.4 months and 9.5 months for pazopanib and sunitinib, respectively [6].

1.3 Next Generation Targeted Treatments

Cabozantinib: Meteor, Cabosun studies

A number of additional clinical trials have evaluated new targeted therapies for renal cell carcinoma in the adjuvant setting after surgical resection as single-line therapies. One of them is cabozantinib, an oral TKI targeting MET, VEGFRs and AXL.

The phase III Meteor trial comparing cabozantinib with everolimus in patients with advanced RCC and showed superior efficacy and safety in all groups evaluated: <65 (n=394), 65-74 (n=201) and > ≥75 years (n = 63) [7]. Patients, who must have had prior therapy with a VEGFR TKI and exhibited 6 months of progression were deemed eligible, and were randomized 1:1 with a 60 mg once daily administration of cabozantinib and 10 mg once daily of everolimus. Cabozantinib demonstrated greater PFS with hazard ratios of 0.53, (95% CI 0.41–0.68) 0.53 (95% CI: 0.37–0.77); and 0.38 (95% CI: 0.18–0.79) for <65, 65–74 and ≥75 years, respectively. OS HRs were also observed to be significant, being 0.72 (95% CI: 0.54–0.95); 0.66 (95% CI: 0.44–0.99) and 0.57 (95% CI: 0.28–1.14). The ORRs were 15% vs 5%, 21% vs 2% and 19% vs 0% for cabozantinib versus everolimus, respectively [7]. Safety profiles were similar across all subgroups in terms of Grade III/IV AEs, with more frequent occurrences of fatigue and hypertension in the cabozantinib arm. Treatment discontinuation or dose reductions were more common in older patients, especially in the ≥75 years cohort [7].

The METEOR trial was motivated by the absence of data outcomes in patients aged 65 or greater, which although representing half of patients newly diagnosed patients with RCC, and are comprised of only a small proportion of phase III advanced RCC clinical trials. Other targeted therapies for advanced RCC patients have presented with greater efficacy, however for younger subgroups of patients.

The Meteor trial was followed by the Alliance A031203 Cabosun trial, which also evaluated cabozantinib. Cabosun compared the health-related quality of life of patients treated with cabozantinib versus sunitinib in advanced renal cell carcinoma patients who had no prior treatments [8]. Their malignancies were considered poor or intermediate risk for enrollment and evaluation in a randomized, open-label, phase 2 trial. A total of 150 patients received treatment with either cabozantinib (n=78) or sunitinib (n=72). Males comprised 78% of the intent-to-treat population and other patient characteristics were ECOG scores of 0 (45.9%) or 1 (41.4%). Patients had either intermediate (81%) or poor-risk (19%) disease, while 36% exhibited bone metastasis [8].

Approximately 81% of patients had intermediate-risk. Daily dosing was 60 mg/day of cabozantinib and 50 mg/day of sunitinib in a 1:1 randomization. Treatment was discontinued upon progression of disease, therapy intolerance, or voluntary withdrawal or death [8].

Cabozantinib belongs to a class of tyrosine kinase inhibitors targeting VEFG, MET and AXL. It received prior approval in 2016 by the FDA for advanced renal cell carcinoma patients who had no previous antiangiogenic treatments. Evaluable criteria included 3 health states, time spent without toxicity before progression of disease or TWiST, time spent with toxicity before progression of disease, or TOX, and time after disease relapse or REL, progression to death. A summative measure of these durations is Q-TWiST, which is the sum of the mean time in each state. Kaplan-Meier survival curves were generated for each treatment arm and assessed for TWiST, REL and TOX by assessing the area under the curve. (Figure 2).

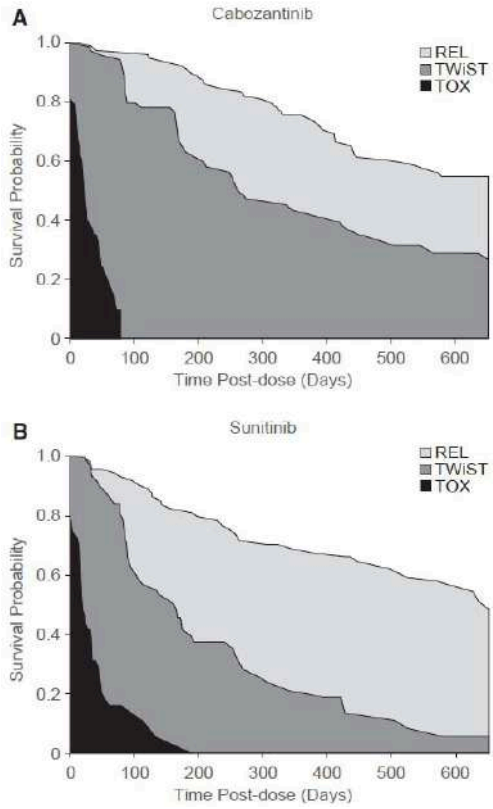

Figure 2: Kaplan-Meier Survival Curves for cabozantinib (top) Versus Sunitinib (bottom) (adapted from Chen et al) [8]

According to the data revealed by the study, mean days were 317 days (cabozantinib) and 180 days (sunitinib) for TWiST with a mean days difference of 137 days and a 95% CI of 60-214. Data for TOX were 31 days (cabozantinib) and 39 (sunitinib) with a mean days difference of -8 and a 95% CI of -25 to 9. REL results were 154 (cabozantinib) and 259 (sunitinib) with a means difference in days of -105, and a 95% CI of -206 to -5 [8].

The study authors demonstrated statistical significance for Q-TWiST differences in patients with advanced RCC, which were observed to be of longer duration for cabozantinib versus sunitinib, (+ 92 (95% CI 5-178 days) and +137 (95% CI of 6-=214 days)), with a difference range of +24 days to +137 days. These results translated into positive health outcomes in terms of quantity and quality of life, with the advantage of cabozantinib conferring extended time for patients prior to cancer progression [8].

Axitinib has also emerged as a VEFGR targeted agent in the second line setting. In the AXIS study, axitinib was compared to sorafenib and PFS served as the primary endpoint. Axitinib was administered after treatment with bevacizumab plus interferon-alfa, temsirolimus, (mTOR inhibitor) or cytokine therapy. PFS was 6.7 and 4.7 months for axitinib and sorafenib respectively ($p < .0001$) [3].

Other novel investigational compounds were evaluated in mRCC patients, however with inconclusive results. In a randomized phase II study a novel antibody-drug conjugate called AGS-16C3F that targets a cell-surface ectonucleotide pyrophosphatase/phosphodiesterase 3 (ENPP3) conjugates to a microtubule disruptive agent: The primary endpoint of investigator-assessed PFS was not met when AGS-16C3F was compared to heavily pretreated mRCC patients with any histology and stage of disease progression [9]. Patients randomized 1:1 received the investigational compound intravenously at 1.8 mg/kg every three weeks or oral axitinib at a starting dosage of 5 mg twice daily. Out of 133 patients, 84 reached data cutoff, and the median PFS were 2.9 months and 5.7

months for AGS-16C3F and axitinib respectively (HR 1.676; 95% CI 1.107-2.537). OS was the secondary endpoint, and there was similarly no significant differences among cohorts observed. Adverse events ranged from fatigue (53%) and nausea (47%) in the AGS-16C3F cohort and similar trends (fatigue 57%; diarrhea 48%) in the axitinib arm, which were expected for both targeted therapies from previous studies. However, ocular toxicities were more common in the patients receiving AGS-163F versus axitinib (48% and 17% respectively) [9]. The study investigators concluded "[t]he investigational compound, AGS-16C3F, did not meet the primary endpoint of this trial," and further studies are not expected to be conducted in this patient population. [9]

As shown, these single-line agents have met primary endpoints in clinical trials and led to antitumor activity in RCC patients, and demonstrate "modest efficacy" as monotherapies and have led to increased resistance that develop as a result of dual feedback mechanisms that inactivate the von Hippel-Landau gene, implicated in tumor aggressiveness and poor survival outcomes for RCC, particularly clear-cell RCC. Also, these small molecule TKIs, such as sunitinib, sorafenib, and pazopanib, have multiple targets and inhibit more than ten targets with non-specificity, resulting in shorter duration of therapy at the maximum tolerated dose, thus impacting the their potential as optimal therapies.

A third generation agent, tivozanib, a selective VEGFR inhibitor, was compared to sorafenib in a phase 3 trial in treatment-naïve RCC patients exhibiting metastasis. A mPFS of 11.9 months was elicited for tivozanib in comparison to sorafenib with a mPFS of 9.1 months (HR, 0.80; 95% CI, 0.63-0.99; P5.04). However, OS demonstrated longer survival in the sorafenib cohort: (29.3 vs 28.8 months; HR, 1.24; 95% CI, 0.95-1.62; P5.1.05), which led to the Food and Drug Administration (FDA) to deny approval for the tivozanib. [3]

HIF Inhibitors

Other new agents under development are a class of small molecule inhibitors that target HIF directly, which occurs upstream of angiogenesis activation. One of the first compounds studied in this category is the "first-in-class HIF-2α inhibitor PT2385" that was evaluated in a phase I trial on previously treated clear cell mRCC patients that demonstrated a favorable safety profile and a significant ORR of 14% [2]. Another agent MK-6482 in the same category as PT2385 (but constituting a second-generation agent) was evaluated in a phase I/II study in a patient population with clear cell mRCC and elicited significant ORR (24%) and mPFS (11.0 months). The efficacy of this agent was evaluated with mTOR inhibitor everolimus in previously treated mRCC patients and is undergoing investigation in a phase III study [2].

Novel investigational therapies have been developed that target rare alterations in RCC. One has been discovered and is based on the identification on several fusion partners with ALK, including VCL, TPM3, and EML. Results on the targeted therapy administration of entrectinib (RXDX-101) were reported by Tao et al [10]. Entrectinib is an agent that targets the VCL-ALK fusion, a rare mutation in RCC patients. 517 samples derived from 561 RCC patients underwent mutational profiling through broad, hybrid capture-based next-generation sequencing (NGS) using the Integrated Mutational Profiling of Actionable Cancer Targets assay and HiSEquation 2500 (Illumina, San Diego, CA) [10].

A total of three patients or 0.6% out of this cohort were found to harbor ALK fusions. One of these three patients was eligible for clinical trial enrollment investigating the efficacy of entrectinib, a targeted agent against ALK. A primary tumor was found through NGS to have a VCL-ALK translocation that generated a novel fusion gene between exon 16 of VCL and exon 20 of ALK. IHC validated the detection of ALK overexpression; FISH confirmed the fusion gene. The authors hypothesized that the existence of this VCL-ALK rearrangement in this patient would respond to first-line systemic therapy with an ALK inhibitor, such as entrectinib, and the patient was enrolled in a clinical trial of entrectinib (RXDX-101) [10]. This patient was a

22-year old male with clinical presentation of anemia and hematuria. A heterogeneous mass was detected through CT that completely replaced the right renal parenchyma. Nephrectomy was performed, revealing a RCC that exhibited pleomorphic features and metastasis of lymph nodes. Tumor resection was successful and CT confirmed no recurrence 2 months later [10].

According to Tao et al, "The patient enrolled on the 600-mg/d dose escalation cohort of the phase I and IIA clinical trial of entrectinib (RXDX-101) and received mentrectinib 600 mg orally per day. Response, assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, was monitored by computed tomography (CT) imaging performed at baseline, 4 weeks after treatment initiation, and approximately every 8 weeks thereafter. Treatment was administered until the patient experienced disease progression or unacceptable toxicity. Permission to publish the patient's case was obtained from his health care proxy." [10]

"Four weeks after commencing entrectinib 600 mg per day, a CT scan demonstrated a 31.4% decrease in disease, or partial response. With continued therapy, the patient attained a 61.9% decrease in disease by 15 months. The patient maintained excellent performance status throughout treatment, tolerating entrectinib well with the exception of grade 1 peripheral lower extremity edema and grade 2 weight gain. His response to entrectinib continued for 19 months, after which imaging revealed radiographic disease progression with increased mediastinal adenopathy, which led to the discontinuation of entrectinib."[10]

1.4 Combination Approaches for clear cell Renal Cell Carcinoma

Combination approaches have met with success in the RCC therapeutic area. One evaluated a potential TKI-mTOR regimen. The phase 3 trial INTORSECT compared the efficacy of sorafenib and temsirolimus in a second-line setting in 512 advanced RCC patients who progressed on sunitinib. mPFS, the primary endpoint, were 3.9 months and 4.3 months in the combination and comparator arms, respectively (HR, 1.31; 95% CI, 1.05-1.63; P5.01). [3]

Other combination regimens evaluated in clinical trials have increased options for clinicians, such as phase 2 TORAVA and phase 3 INTORACT studies evaluating bevacizumab plus temsiro limus, or bevacizumab plus sunitinib, or any mTOR inhibitor with sunitinib. These studies have shown and demonstrated superior efficacy and safety profiles. [5] A randomized combination study, CROSS-J-RCC, conducted by Tomita et al, compared sunitinib and sorafenib as front-line agents in the treatment of metastatic ccRCC. In this open-label trial, treatment-naïve metastatic clear cell renal cell carcinoma patients (n=120) with favorable or intermediate MSKCC risk were randomized to receive sunitinib followed by sorafenib or sorafenib followed by sunitinib. The primary endpoint of mPFS observed was 8.7 months and 7.0 months (HR 0.67; 95% CI 0.42-1.08) for the SU/SO and SO/SU groups, respectively [6]. Total PFS and OS served as secondary endpoints and demonstrated superiority of total PFS for the SU/SO subgroup upon analysis in patients with favorable MSKCC risk (27.8 and 22.6 months; HR, 0164; 95% CI, 0.035-0.766). However, in contrast, the HR was 11.816 (95% CI 1.355-103) in the SO/SU in patients without prior nephrectomy.

CROSS-J-RCC is particularly relevant because it included a population of intermediate risk patients who have not been closely studied prior to this study, and reflects on other prominent studies that focused on targeted agents in mRCC patients with poor prognostic factors [6].

The safety profile indicated that for the median duration of treatment for sunitinib and sorafenib was 6.7 months and 6.1 months, respectively, at data cutoff. Hand-foot syndrome, anorexia, fatigue and hypertension was seen as the most frequent AEs for sunitinib and HFS, hypertension, fatigue and stomatitis was observed as frequently occurring AEs for sorafenib. Abnormal laboratory values such as neutropenia, proteinuria and increased lipase were observed for sunitinib, while increased lipase, increased aspartate transaminase, increased alanine transaminase,

and thrombocytopenia were observed with sorafenib. [6].

A new VEGFR TKI has emerged with greater efficacy at its maximum tolerated dose with less adverse events: X-82, CM082 or vorolanib, a highly potent VEGFR/PDGFR TKI. Vorolanib is a novel kinase inhibitor that is "indolinone-based" and targets VEGFR, PDGFR and Colony Stimulating Factor 1 Receptor (CSF1R), but simultaneously exhibits low inhibition on RET and AMPK. Due to this innovative specificity, vorolanib has the potential to have a better safety profile and a large therapeutic window. In fact, in a phase 1 trial, patients tolerated this agent well at a dosage administration range from 20 to 400 mg taken daily at doses that did not reach the most tolerated dose. TRAEs ranged from nausea, fatigue, to diarrhea and vomiting in were reported in one study, while leukopenia, fatigue and hypertension were observed in another trial, however not reaching dose-limited toxicity. This led investigators to hypothesize that vorolanib when combined with mTOR target everolimus could augment antitumor activity by targeting both pathways and achieve tolerable side effect [5]. A phase I study was performed by Sheng et al. to evaluate this combination regimen and determine safety and maximum tolerated dose (MTD). Patients who had prior treatment with at least one VEGFR-TKI, such as first-line sunitinib, sorafenib, pazopanib, anlotinib and famitinib as well as second-line anlotinib, sorafenib and sunitinib were considered eligible and were administered at least one dose of the combination therapy. Table 1 shows the treatment-related adverse events; MTD was not achieved consistent with other trials in USA and China evaluating vorolanib as a monotherapy.

Table 1: Reported Adverse Event and their Incidences Associated with Vorolanib (Adapted From Sheng Et Al) [5]

	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Proteinuria	22 (100.0)	1 (4.5)	0 (0)
Leukopenia	17 (77.3)	4 (18.2)	0 (0)
Hypercholesterolaemia	17 (77.3)	1 (4.5)	0 (0)
Increased low-density lipoprotein	15 (68.2)	0 (0)	0 (0)
Hair color change	15 (68.2)	0 (0)	0 (0)
Hypertriglyceridaemia	14 (63.6)	4 (18.2)	2 (9.1)
Neutropenia	14 (63.6)	2 (9.1)	0 (0)
Raised blood glucose	13 (59.1)	0 (0)	0 (0)
Fatigue	12 (54.5)	0 (0)	0 (0)
Hypertension	11 (50.0)	4 (18.2)	1 (4.5)
Creatine phosphokinase elevation	11 (50.0)	0 (0)	1 (4.5)
AST elevation	10 (45.5)	0 (0)	0 (0)
Diarrhea	10 (45.5)	1 (4.5)	0 (0)
Thrombocytopenia	9 (40.9)	1 (4.5)	2 (9.1)
Decreased hemoglobin	9 (40.9)	0 (0)	0 (0)
Mucosal inflammation	9 (40.9)	1 (4.5)	0 (0)
Lid edema	8 (36.4)	0 (0)	0 (0)
Anemia	7 (31.8)	3 (13.6)	0 (0)
Mouth ulceration	7 (31.8)	0 (0)	0 (0)
ALT elevation	5 (22.7)	0 (0)	0 (0)
Decreased appetite	5 (22.7)	1 (4.5)	0 (0)
Peripheral edema	5 (22.7)	0 (0)	0 (0)
Dyspnea	3 (13.6)	0 (0)	1 (4.5)

According to Sheng et al, "Fifteen patients had disease progression (n = 13) or death (n = 2), and the median progression-free survival was 5.6 months (95% Cl: 4.6 13.0). For patients in the 200 mg cohort (n = 13), the ORR and DCR was 38.5% (95% CI: 14 68%) and 100% (95% CI: 75 100%), respectively, and the median PFS was 5.7 months (95% Cl: 4.8 16.7) (Fig. 4(a)). Among

the 8 patients treated with only one prior VEGFR TKI, the median progression-free survival was 10.2 months (95%CI: 3.7 16.7%). [Eleven] patients had OS events, the median OS was 25.1 months (95% CI 5.9, 49.9) and 25.1 months (95% CI 5.9, NA) for all patients and those in the 200 mg cohort, respectively [5]."

1.5 Recent Clinical Trials: anti-PD-1/PD-L1 agents for ccRCC

In open-label, randomized, phase 3 CheckMate 9ER, nivolumab plus cabozantinib was shown in first line treatment vesus sunitinib to have superior PFS, OS and ORR when evaluated after long-term follow-up results of 18.1 months, reporting updated safety and efficacy. The patient population was untreated and had measurable disease according to RECIST assessed by the investigator with PD-L1 testing conducted. Patients received nivolumab with cabozantinib (n=323) and sunitunib (n=328) in a random 1:1 assignment that was stratified by PD-L1 expression, among other factors. PFS by blinded independent central review was the primary endpoint and OS was the secondary endpoint. Updated mPFS was 16.6 months (12.8-19.8) iversus 8.3 months ((7·0-9·7; HR 0·56 [95% CI 0·46-0·68]. mOS was 37.7 months (95% CI 35.5 to NE) in the nivolumab plus cabozantinib group veruss 34.3 months in the sunitinib group (29.0 to NE) (hazard ratio [HR] 0·70 [95% CI 0·55-0·90], p=0·0043. Adverse events included hypertension (13% or 40) of 320 patients in the nivolumab and cabozantinib group and 12% or 39 of 320 in the sunitinib group and diarrhea 7%[22] versus 5%(15) in the sunitinib cohort, with grade 3-4 TRAEs in 22% or 70 of 320 patients and 10%(31) of 320 patients in the nivolumab with cabozanitinib and sunitinib cohorts respectively. [13]

In the phase 3, double-blind, 1:1 randomized KEYNOTE-564 trial overall survival results were reported for adjuvant pembrolizumab in ccRCC and was approved on the basis of marked disease free survival. Patients enrolled had an increased risk of recurrence and showed a significant increase according to investigator assessed DFS, the primary endpoint. OS and safety were secondary endpoints. The HR for DFS was 0.72 (95% CI, 0.59-0.87) and OS was 91.2% in the pembrolizumab cohort and 86.0% in the placebo group with benefit observed across subgroups. No deaths occurred as a result of the pembrolizumab and grade 3 or 4 adverse events were 20.7% versus 11.5%. The study showed that adjuvant pembrolizumab was associated with clinically meaningful improvement in OS. [14]

In LITESPARK-005, phase 3, multicenter, open label trial, belzutifan, a HIF 2-alpha inhibitor showed clinical activity in early phase studies when evaluated against everolimus. Of the 374 patients assigned to belzutifan in a dosage of 120 mg versus 10 mg of everolimus administered once daily, a significant part of the cohort showed improvement in PFS and OS, the primary endpoints, and the occurrence of objective response (ORR), the secondary endpoint. PFS was reported as 24% in the belzutifan group versus 8.3% in the everolimus, demonstrating cancer free of progression. ORR was 21.9% (95% confidence interval [CI], 17.8 to 26.5) versus 3.5% (95% CI, 1.9 to 5.9) in the belzutifan and everoliumus cohorts respectively. mOS was 21.4 months versus 18.1 months, with 55.2% versus 50.6% of participants being alive (hazard ratio for death, 0.88; 95% CI, 0.73 to 1.07. Grade or higher side effects were higher in the everolimus group (62.5%) versus 61.8% in the belzutifan group, with treatment discontinuation occurring in 5.9% versus 14.7%, in the respective cohorts (belzutifan versus everolimus). The authors concluded that the clinical benefit of belzutifan was shown for advanced ccRCC patients who had prior therapy with immunotherapies or antiangiogenic therapies, and the treatment was associated with "no new safety signals." [15]

II. DISCUSSION

In the precision medicine era, targeted therapies for clear cell RCC have met with varied success, and while many have been shown to present with clinical activity, some outcomes of clinical trials have been modest, or even less than modest. ASSURE and S-TRAC were the first trials to evaluate sunitinib and sorafenib vs placebo presented with relatively disappointing results.

Surtime presented with data that neoadjuvant sunitinib after immediate cytonephrectomy (CN) did not have statistically significant mPFS and OS when compared to deferred CN [11]. However, when patients analyzed on an efficacy trial who progressed on IO-VEGF therapy and received a number of subsequent targeted therapies in a phase III study, Including cabozantinib, axitinib, pazopanib, lenvatinib, sunitinib, and sorafenib, post-IO-VEGF ORR was "25% and median PFS was 12.0 months (95% CI, 8.2–24.5) while the median OS was 24.5 months (95% CI, 12–NE) and 12 months OS rate was 63.3% (95% CI, 48.6–74.9) [12]."

Other complexities arise in the targeted treatment of RCC when considering the benefits of mTOR inhibitors versus VEGFR-TKI inhibitors. Evidence of the efficacy of mTOR inhibitor compared with a TKI in the first-line setting was elucidated in the phase 2 RECORD-3 trial. PFS served as the primary endpoint was reported as 7.9 months and 10.7 months for everolimus and sunitinib respectively (HR, 1.4; 95% CI, 1.2-1.8), and was not met, but did imply that TKIs had noninferiority over mTOR inhibitors, putting into question the clinical benefit of a monotherapy mTOR inhibitor such as everolimus. [3)

Further complicating the predictive analysis of RCC was evidence that everolimus actually harbored the PTEN genomic alteration rather than being involved in the mTOR pathway, a hypothesis tested in patients enrolled in the same RECORD-3 trial. Targeted NGS was employed to analyze archival specimens collected at baseline to detect mTOR pathway components, while IHC assessed PTEN expression. When everolimus-treated patients were evaluated for PTEN expression through IHCC, 50 patients who retained PTEN expression versus 50 patients who lost PTEN expression had a mPFS of 5.3 months versus 10.5 months respectively (HR, 2.5;

P < 0.001). These differences were not duplicated in the sunitinib arm (10.9 months vs. 10.3 months; HR, 0.8; P= 0.475). The investigators concluded that the "[a]ssociation between mutation status for [mTOR] and therapeutic outcome on everolimus was not confirmed. Clinically meaningful differences in PFS were seen based on PTEN expression by IHC, lost in >50% of patients."[16]

Additionally, in vitro assays have identified actionable targets for kidney cancer that overcome drug resistance. Porcupine (PORCN) has been shown to play a role as a palmitoyltransferase that affects the activation and secretion of the WNT pathway through transcription of Wnt proteins [14]. Li et al found high expression of PORCN in renal cancer cell lines that have poor prognosis, and that PORCN expression occurred concomitantly with expression of Wnt proteins. LGK974, an investigational agent, was found to inhibit tumor cell growth and promote apoptosis in ccRCC cells, and prevent metastasis by reducing the expression of mesenchymal markers in a study conducted by Li et al [14]. (Figure 3 and Figure 4).

They found that "After treatment with LGK974, the expression level of β-catenin, a key protein in the classical Wnt pathway, was significantly decreased, and the expression levels of the target genes cyclin D1, c-Myc, MMP9, and MMP2 in the Wnt signaling pathway were also significantly decreased, which represented a significant decrease in the activity of the Wnt signaling pathway." Concurrently, the cell cycle of renal cancer cells was blocked significantly, and the authors concluded that "our results indicate that LGK974 could significantly inhibit the progression of renal cancer cells in a safe concentration range, so PORCN may be a safe and effective target for patients with renal cancer" [17].

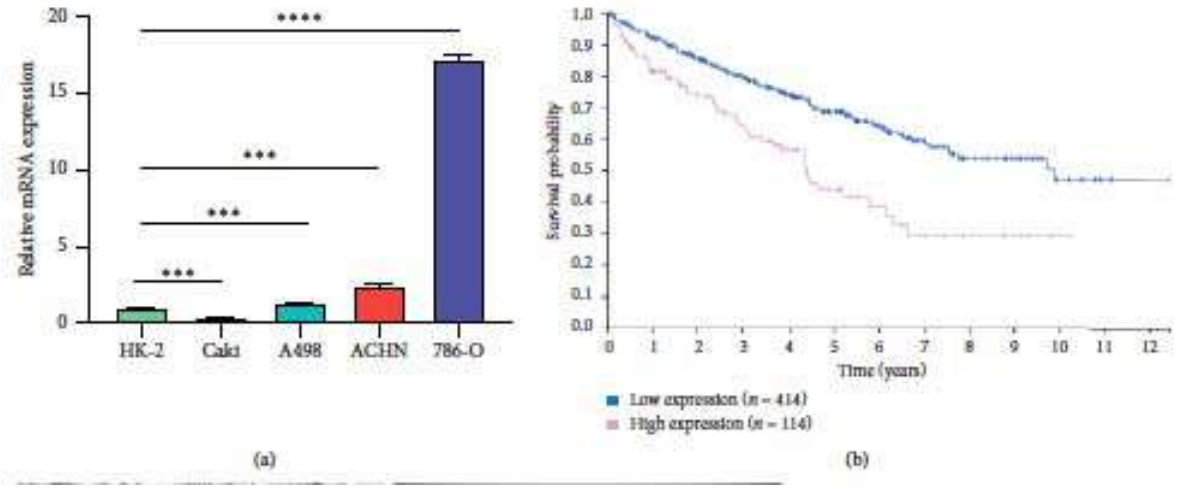

Figure 3: Relative miRNA Expression as an Indicator of Survival Probability (adapted from Li et al) [15]

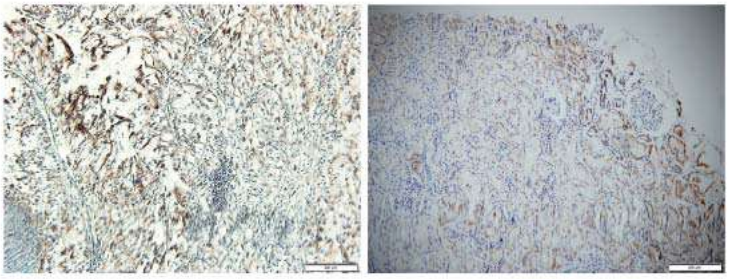

Figure 4: Mesenchymal Markers in Cancerous Tissue Versus Normal Cells (adapted from Li et al) [15]

Finally, predictive tissue biomarkers have emerged from recent studies revealing upregulated gene signatures that predict the efficacy of treatments and open the door for liquid biopsy and circulating tumor DNA-targeted sequencing options [1]. According to Signoretti et al in a report published in the *Journal of Clinical Oncology,* targets such as proangiogenic VEGF and PDGF that are implicated in the VHL-HIF pathway as a result of VHL inactivation could serve as predictive biomarkers for determining the clinical responses of VEGF-targeted therapy. These biomarkers include HIF-1a and HIF-2a and the authors cite a study by Hsieh and colleagues that "evaluated the association between somatic gene mutations and treatment outcomes in a randomized trial comparing first-line sunitinib with everolimus in patients with mRCC" [1]. In the RECORD-3 trial, it was found that PBRM1 mutations were associated with longer PFS in the everolimus cohort, and likewise with KDM5C mutations in the sunitinib arm. It was later found in an analysis of the phase III COMPARZ trial that compared pazopanib with sunitinib in patients with locally advanced or metastatic RCC that high PBRM1 mutant tumors were associated "significantly improved OS and PFS compared with the PBRM1 nonmutant group. [1]" The authors note that this finding implicating PBRM1 alterations as a predictive biomarkers for VEGFR targeted therapy is "intriguing" since PBRM1 codes for BAF180 ("a subunit of the PBAF subtype of the switch-sucrose nonfermentable chromatin remodeling complex"), and occurs with inactivation of VHL that are both dependent on the signaling of HIF and are more sensitized to antiangiogenic agents that are "directed against the HIF target VEGF." [1]

The authors continue that "In an exploratory analysis of the IMmotion 150 trial, the expression of six angiogenesis-associated genes was identified as a potential predictive marker of response to sunitinib." In the COMPARZ trial, a

different gene signature associated with the antiangiogenic agents exhibited longer PFS and OS in sunitinib or pazopanib treated patients. However, the value of PBRM1 biomarker along with the gene signatures as predictive biomarkers needs to be confirmed through further independent validation in large controlled clinical studies and future "[l]arge-scale transcriptome profiling of pretreatment ccRCC tissues has contributed to the recent identification of transcriptional signatures that might be useful in predicting clinical benefit from VEGF-targeted agents" [1].

The authors end by caveating that these analyses were conducted on patient cohorts that were limited in size, and technical issues abound in terms of experimental protocols and interobserver variability, but conclude optimistically as "larger independent and more controlled studies are needed to further clarify the significance of these findings," since "these older studies mostly relied on single-gene sequencing and single-marker immunohistochemical stains, the recent implementation of new sequencing technologies has provided a platform for large-scale biomarker discovery." [1]

III. CONCLUSION

Treatment for RCC has made significant advances from its origins in hormonal and chemotherapy through the use of immunomodulatory agents and the evolution of targeted therapy options. Targeted therapy has established itself as having robust outcomes in clinical settings evaluating VEGFR-TKIs and mTOR inhibitors and other newer third-generation and investigational agents for high-risk poor prognostic patients. While some results were modest, overall the outlook has been improved for RCC patients, especially the ccRCC molecular subtype. As recent studies have confirmed ICIs as viable therapies, future studies may explore therapies combining ICIs with VEGFR-TKIs, mTOR inhibitors and even newer agents that have shown clinical efficacy such as vorolanib and entrectinib. Clinicians can now be cautiously optimistic for treatment of patients with RCC.

Declarations

Abbreviations

ccRCC: Clear Cell Renal Cell Carcinoma
CI: Confidence Interval
CSF1B: Colony Stimulating Factor 1 Receptor
CT: Computed Tomography
DFS: Disease Free Survival
HD IFN: alpha High-Dose Interferon-Alpha
HIP: Hypoxia-Inducible Pathway
ICI: Immune Checkpoint Inhibitor
IL: Interleuken
IMDC: International mRCC Database Consortium
mPFS: Median Progresssion Free Survival
MSKCC: Memorial Sloan Kettering Cancer Center
MTD: Maximum Tolerated Dose
mTOR: Mammalian Target of Rapamycin
ORR: Overall Response Rate
PDGFR Platelet: Derived Growth Factor Receptor
PFS: Progression Free Survival
RCC: Renal Cell Carcinoma
SO: Sorafenib
SU: Sunitinib
TKI: Tyrosine Kinase Inhbitor
TRAEs Treatment: Related Adverse Events
VEGFR: Vascular Endothelial Growth Factor Receptor
VHL: von Hippel-Landau

Ethics Approval and Consent to Participate

Not Applicable

Consent for Publication

Not Applicable

Availability of Data and Material

Not Applicable

Competing Interests

The author has stock ownership in Novartis, Merck, Eli Lilly and Bristol-Myers Squibb.

Funding

Not Applicable

ACKNOWLEDGEMENTS

Not applicable.

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Review of Mortality Patterns in Korle Bu Teaching Hospital's Emergency Department Over One Year

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ABSTRACT

Background: Mortality trends in Emergency departments serve as vital indicators of healthcare quality and system effectiveness. Understanding the mortality patterns in these settings is crucial for optimising emergency care delivery. However, limited research exists on mortality trends in emergency departments, particularly in low-resource settings such as Ghana. This study seeks to provide valuable insights into the factors contributing to mortality and inform strategies for improving emergency care. This study aimed to analyse mortality trends in the Emergency Department of Korle-Bu Teaching Hospital in Ghana over a specified period.

Keywords: mortality, emergency department, attendance, admissions, brought-in-dead.

Classification: DDC Code: 62N01

Language: English

LJP Copyright ID: 392844

Great Britain Journals Press

London Journal of Medical & Health Research

Volume 25 | Issue 6 | Compilation 1.0

Review of Mortality Patterns in Korle Bu Teaching Hospital's Emergency Department Over One Year

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ABSTRACT

Background: Mortality trends in Emergency departments serve as vital indicators of healthcare quality and system effectiveness. Understanding the mortality patterns in these settings is crucial for optimising emergency care delivery. However, limited research exists on mortality trends in emergency departments, particularly in low-resource settings such as Ghana. This study seeks to provide valuable insights into the factors contributing to mortality and inform strategies for improving emergency care. This study aimed to analyse mortality trends in the Emergency Department of Korle-Bu Teaching Hospital in Ghana over a specified period.

Methodology: This retrospective study utilised data obtained from medical records of patients who presented to the emergency department of Korle-Bu Teaching Hospital and subsequently died during their hospital stay for the year 2023. After obtaining ethical approval, data on patient demographics (such as age and sex), admission records, clinical characteristics, and diagnoses were collected, analyzed, and presented using descriptive statistics.

Results: During the review period, the total attendance at the KBTH Accident and Emergency Centre was 14,472, comprising 8,666 males and 5,806 females. Among these attendees, 5,856 individuals were admitted. The centre reported 492 cases of Brought-in-Dead (Dead on Arrival). The age group with the highest attendance was 15-44 years. A total of 909 deaths occurred in the emergency department, with 465 males and 444 females. The age distribution of fatalities showed the majority occurring in the 60+ age group. The overall mortality rate per attendance was 6.3%. The leading cause of death was cerebrovascular accident (CVA), followed by chronic renal disease and all types of pneumonia.

Conclusion: The review of mortality patterns offers valuable insights into the epidemiology, outcomes, and challenges associated with emergency care. These findings underscore the importance of ongoing surveillance, quality improvement initiatives, and interdisciplinary collaboration to enhance patient care and inform health promotion strategies in communities aimed at reducing mortality.

Keywords: mortality, emergency department, attendance, admissions, brought-in-dead.

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I. INTRODUCTION

The Emergency Department (ED) is the primary gateway to any hospital and is critical in providing immediate medical care to patients with acute injuries and illnesses (1)(2)(3). Emergency care encompasses medical decision-making and the skills or competencies required to avert unnecessary mortality or disability (4). These competencies involve swiftly assessing, resuscitating, and stabilizing patients facing life- or limb-threatening conditions (4).

Mortality trends within Emergency departments serve as important indicators of the quality of emergency healthcare services and can help identify areas for improvement. Mortality rate and its associated spectrum are key health indicators requiring regular assessment in any healthcare facility (1). The emergency department

serves as a vital hub for treating patients with diverse medical and surgical conditions of varying severity, facilitating interventions to correct physiological abnormalities and mitigate the progression of organ failure, thereby reducing mortality rates (3).

Conducting mortality audits in the emergency department is particularly crucial as it sheds light on various aspects, including the range of emergency cases prevalent in the community, the burden of morbidity, the demographic distribution, the efficacy of the emergency department's response, and the mortality load (1). Additionally, the profile of cases observed in the emergency department is reflective of the prevalent risk factors and disease patterns within the community (5).

Ghana, like many other low- and middle-income countries, faces unique challenges in delivering emergency medical care due to resource constraints, lack of an efficient prehospital care and transport system, severity of illness or injury, and limited access to specialized services all contributing to increase in in-hospital mortality (3). Despite efforts to strengthen healthcare systems, gaps in emergency care provision persist, contributing to adverse outcomes, including high mortality rates in emergency departments (6). The lack of comprehensive data on mortality trends and associated factors in Ghanaian Emergency departments hinders the development and implementation of targeted interventions to address this issue. Therefore, investigating hospital mortality trends is crucial for understanding the local context and informing evidence-based strategies to enhance emergency medical services. This study explores mortality trends in the Accident and Emergency Department of Korle Bu Teaching Hospital, Ghana's largest referral centre, which serves the southern region and receives a high volume of patients.

II. MATERIALS AND METHODS

This was a retrospective review of the digital data records of all patients who presented to the accident and emergency centre from 1 January 2023 to 31 December 2023 to receive care. The mortality data was collected over one year to provide a focused snapshot of the patterns and trends within a defined and recent timeframe. All patients who presented to the Accident and Emergency Centre to seek care over the specified period and died during their hospital stay were included. Ethical approval was sought from the Korle Bu Scientific Technical Committee and Institutional Review Board for the study (KBTH-IRB 00077/2024).

The Korle Bu Teaching Hospital is Ghana's largest and leading referral centre. With a bed capacity of 2000, it primarily serves the southern part of the country as a major referral hospital. It comprises 17 clinical and diagnostic departments, including the Accident and Emergency Centre, which functions as the receiving point for trauma, medical, and surgical emergencies.

The Accident and Emergency Centre comprises a triage area and three main wards (Red, Orange, and Yellow), categorised by illness acuity using the South African Triage Scale (SATS). Based on their Triage Early Warning Scores (TEWS), patients are colour-coded: Red (TEWS >6) for life-threatening emergencies, Orange (TEWS 5-6) for very urgent cases, and Yellow (TEWS 3-4) for urgent cases, while Green (non-urgent) cases (TEWS 1-2) are directed to the Korle-Bu Polyclinic. Red, Orange, and Yellow patients are admitted into the respective wards, managed by emergency medical officers and residents under specialist supervision, and referred to relevant specialties for continued care. The Clinical Decision Unit (CDU) serves as an overflow ward for the emergency department.

Records of all deceased patients who died whilst on admission at the Accident and Emergency were retrieved and organized by month. Data was extracted from the patient's electronic record system (Lightwave Health Information Systems (LHIMS)). This is the hospital's digital health platform for patients' data and clinical records.

For patients with incomplete electronic records, data were manually reconciled using ward admission and discharge registers maintained by

ward nurses. All patients who died in the emergency department during the specified period were included in the analysis.

The variables collected included age, sex, clinical diagnosis (primary working diagnosis), duration of stay (in hours), and possible cause of death based on the primary clinical or working diagnosis in patient's records. Patients brought in Dead (BID) or dead-on arrival were included. Data obtained was entered into a Microsoft Excel data capture sheet, organized by months of the year, and then cleaned. Descriptive statistics were used to calculate the total number of admissions and deaths, with the results presented as frequencies and percentages in tabular form.

III. RESULTS

During the review period, the total attendance at the KBTH Accident and Emergency Centre was 14,472, comprising 8,666 males and 5,806 females, resulting in a male-to-female ratio of 1.5:1. Among these attendees, 5,856 individuals were admitted and an additional 1,456 were detained. The centre reported 492 cases of Brought in Dead (Dead on Arrival), yielding an incidence rate of 3.4%. The age group with the highest attendance was 15-44 years, with a mean age of 42.16 (Table 1).

A total of 909 deaths occurred in the emergency department, with 465 males and 444 females (Figure 1). The highest number of deaths occurred in January, followed by December. The age distribution of deaths is detailed in Table 1, with the majority occurring in the 60+ age group. The mean age was 52.66. The overall mortality rate per attendance was 6.3%.

Of the 5,856 admitted patients, 1,866 were admitted to the red ward, 1,928 to the orange ward, 1,641 to the yellow ward, and 424 to the Clinical Decision Unit (CDU). Table 2 presents the distribution of deaths per ward, with the red ward accounting for the highest fatalities (65.79%). The mortality rate per admission was 15.52%.

358 deaths (39.39%) occurred within the first 24 hours, increasing to 568 (61.1%) up to 48 hours after admission. Additionally, 341 (37.51%) occurred more than 48 hours after admission (Table 3).

The possible causes of death based on the working clinical diagnoses are listed in Figure 3. The leading possible cause of death was cerebrovascular accident (CVA), followed by chronic renal disease and pneumonia. The leading possible cause of death within the first 24 hours was CVA, followed by Pneumonia (Table 4).

IV. DISCUSSION

The mortality patterns in Korle Bu Teaching Hospital's Emergency Department over one year provide valuable insights into the epidemiology and outcomes of patients presenting to the emergency department (ED). The findings highlight important demographic characteristics, mortality rates, ward distribution, and leading causes of death within the studied population.

The study period encompassed a total attendance of 14,472 individuals at the KBTH Accident and Emergency Centre, with a male-to-female ratio of 1.5:1. This observation aligns with existing literature indicating a higher prevalence of emergency department visits among males compared to females (7)(8)(9). Men are more prone to injuries, making them more likely to present to the emergency department.

The incidence rate of Brought in Dead patients among patient attendance was 3.4% higher than in settings with well-established pre-hospital emergency care systems (10). Although there is no standard definition of brought-in-dead, the broad definition may encompass patients who are either pronounced dead upon arrival at an emergency department without any resuscitation attempt or those who passed away after unsuccessful resuscitation efforts, typically within the first 15 to 60 minutes of arrival (10). In high-income settings with well-established prehospital settings, the BID rate is less than 2% (8). Although our BID rate did not differ so much from established settings, studies of high BID rates in other low-resource settings have been reported.

The study's findings highlight a significant aspect: the noticeable mortality rate observed

within the emergency department. A total of 909 deaths were recorded, with a mortality rate of 6.3% per attendance. Morbidity and mortality rates within the emergency department of any hospital serve as indicators of the adequacy, or lack thereof, of clinical care and infrastructure (11). This underscores the critical nature of conditions managed within the ED and emphasizes the need for prompt and effective interventions to mitigate adverse outcomes. The mortality rates observed were similar to those of other studies. Okoroiwu et al recorded a mortality rate of 4.5% (12).

The age distribution of deaths reveals a higher prevalence among individuals aged 60 years and above, reflecting the increased vulnerability of older adults to acute emergencies. This was a similar finding by Okoroiwu et al (12). Research indicates that the incidence of cardiovascular diseases rises sharply with age, placing older individuals at a higher risk of mortality (13). Additionally, more men died than women, which was similar to other studies (2)(12)(14). In general, females have been found to exhibit lower mortality rates and longer life expectancies compared to males, with males having higher mortality rates from injuries in regions like Africa, Latin America, the Caribbean and Europe (12)(9). Moreover, it has been found that there is a higher prevalence of cardiovascular diseases in men than in women, putting them at higher risks of mortality (15).

In this study, the 15-44 age group had the highest attendance yet reported the third-highest number of deaths. This age group, although more active and exposed to various risk factors, may be more prone to trauma-related injuries, contributing to their high attendance. Additionally, their tendency towards seeking prompt medical care when faced with serious conditions may lead to increased ED visits. Despite high attendance and proactive health-seeking behaviours, the nature of their injuries or conditions, which could be severe or complex, likely contributed to the significant mortality observed in this group.

Analysis of mortality patterns across different months highlights notable variations, with the highest number of deaths occurring in January, followed by December. While seasonal trends in mortality have been documented in various settings, further exploration is warranted to elucidate potential contributing factors, such as climatic variations, infectious disease outbreaks, non-adherence to medications during holiday seasons or holiday-related accidents.

Ward distribution of admissions provides valuable insights into resource utilisation and patient flow within the emergency department. The red ward, which typically accommodates patients with critical or life-threatening conditions, recorded the highest proportion of deaths (65.79%). This underscores the importance of appropriate triage and allocation of resources to optimise patient outcomes, particularly for those with high-acuity presentations.

The leading causes of death identified in the study further highlight the diverse spectrum of medical conditions encountered in the emergency department. Cerebrovascular accidents (CVAs) emerged as the primary cause of mortality, followed by renal diseases and pneumonia. Recent studies strongly indicate that noninfectious diseases are increasingly recognised as significant causes of morbidity and mortality (14). In low- and middle-income countries, it is estimated that over 80% of deaths result from noncommunicable diseases (14). In a study conducted by Ugare et al., the majority of mortalities were attributed to medical causes, with a significant proportion related to terminal cardiovascular diseases (11). This highlights the critical need for early intervention and effective management of chronic and acute cardiovascular conditions to reduce mortality rates in hospital settings. Patient education, community intervention, and health promotion activities targeting non-communicable diseases, particularly cardiovascular diseases, are essential. By increasing public awareness and encouraging healthier lifestyles, we can potentially reduce the burden of these conditions and improve overall patient outcomes.

A significant portion of the deaths, 39.39%, occurred within the first 24 hours of admission and increased to 61.1% up to 48 hours of

admission, highlighting the critical nature of early intervention in emergency settings. This was similar to the findings in Ugare et al study, where 56% of deaths occurred up to 48 hours after admission (11). Potential reasons attributed to these identified deficiencies within the healthcare system include delays in resuscitation and interventions and inadequate monitoring systems (11). Delays in initiating life-saving procedures and interventions can contribute to increased mortality, whilst poor monitoring systems may fail to promptly identify deterioration in a patient's condition, further increasing the risk of adverse outcomes. Addressing these inadequacies is crucial for optimising patient care and reducing mortality rates.

The leading cause of death within this period was cerebrovascular accident (CVA), followed by various types of pneumonia. These findings emphasize the importance of timely and accurate initial assessments and rapid initiation of treatment protocols to improve patient outcomes. The second-highest number of deaths, accounting for 37.51%, occurred more than 48 hours after admission. This suggests that while initial interventions may stabilize patients, a substantial mortality risk remains during the subsequent hospital stay. These findings indicate the need for ongoing, vigilant monitoring and comprehensive management strategies tailored to address the underlying pathophysiology of common acute conditions encountered in the emergency setting beyond the initial 24-hour period, particularly for chronic conditions.

V. LIMITATIONS OF THE STUDY

This study was based on a retrospective review of medical records, which posed limitations in data quality and completeness. Some records were missing, incomplete, or inconsistently documented; however, these gaps were addressed by cross-referencing ward admission and discharge registers maintained by nursing staff. The findings were based on data from a single institution, Korle-Bu Teaching Hospital, which limits the generalizability of the results to other emergency departments within the country in different settings. Variations in healthcare practices, resource availability, and patient demographics can influence mortality trends and outcomes in other locations. The study may be subjected to selection bias as it only included patients who were admitted to the emergency department and subsequently died. This cannot fully represent all cases of in-hospital mortality, as it excludes those outside the emergency department in different wards. Additionally, there could have been reporting bias in the recording of the cause of death, which may have had an impact on the outcome as the study relied solely on the primary working diagnosis as probable cause of death as reported and documented by the doctors who managed the cases.

VI. CONCLUSION

In conclusion, the review of mortality patterns in the Emergency Department of Korle Bu Teaching Hospital offers valuable insights into the epidemiology, outcomes, and challenges associated with emergency care delivery. These findings underscore the importance of ongoing surveillance, quality improvement initiatives, and interdisciplinary collaboration to enhance patient care and optimize outcomes within the emergency setting.

ACKNOWLEDGEMENTS

We acknowledge the support of the Accident and Emergency Centre staff of the Korle Bu Teaching Hospital, Accra, Ghana. The abstract of this paper was submitted for presentation at the African Conference on Emergency Medicine 2024, held in Botswana.

Conflict of Interest

The authors declare no conflict of interest.

Funding

No funding was received.

Contributions of Authors

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Acquisition, analysis, and interpretation of data: Nana Serwaa Agyeman Quao, Janet Naki

Opare, Theophilus Kpakpo Addo, Alberta Ampomah, Anthony Kofi Sakyi Amoah, Queenster Thompson, Malwine Abena Obuobisah.

Drafting of the Manuscript: Nana Serwaa Agyeman Quao, Janet Naki Opare, Theophilus Kpakpo Addo, Alberta Ampomah, Anthony Kofi Sakyi Amoah, Queenster Thompson, Malwine Abena Obuobisah.

Final review of the Manuscript: Nana Serwaa Agyeman Quao, Janet Naki Opare, Theophilus Kpakpo Addo, Alberta Ampomah, Anthony Kofi Sakyi Amoah, Queenster Thompson, Malwine Abena Obuobisah.

Abbreviations

BID- Brought-In-Dead

CDU- Clinical Decision Unit

CVA- Cerebrovascular accident

ED- Emergency Department

KBTH- Korle Bu Teaching Hospital

LHIMS- Lightwave Health Information Management System

SATS- South African Triage Scale

TEWS- Triage Early Warning Score

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Table 1: Total Attendance, Admissions and Deaths

Total Attendance	N=14472
Male	8666
Female	5806
<1	80
1-4	547
5-14	767
15-44	6574
45-59	3192
60+	3312
Mean Age	42.16
Mode	40
95% Confidence Interval (Mean)	41.81-42.50
Total Admissions	5856
Total Detentions	1456
Total Deaths	909
<1	4
1-4	7
5-14	6
15-44	275
45-59	277
60+	340
Mean Age	52.66
Mode	53, 63
95% Confidence Interval (Mean)	51.48-53.84
Mortality Per Attendance	6.3%
Bid	492
% Bid Per Attendance	3.4%

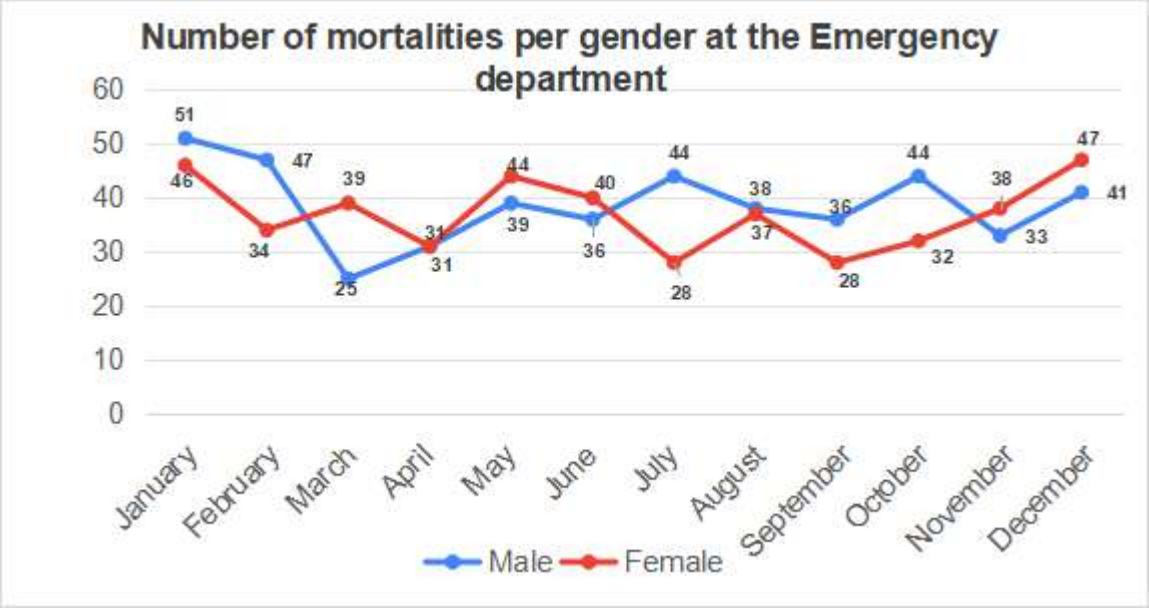


Figure 1: Month and sex distribution

Table 2: Mortality distribution per ward

Ward Name	Total Admissions	Death	%Mortality Per Admissions
Red Ward	1844	595	32.43%
Orange Ward	1928	174	9.02%
Yellow Ward	1641	129	7.86%
Cdu	424	11	2.59%
Total	5856	909	15.52%

Table 3: Duration of stay before death

	Deaths Within 24 Hrs	Deaths > 24 Hrs <48 Hrs	Deaths > 48 Hrs
Red	262	145	188
Orange	66	35	73
Yellow	30	29	70
Cdu	0	1	10
Total	358	210	341

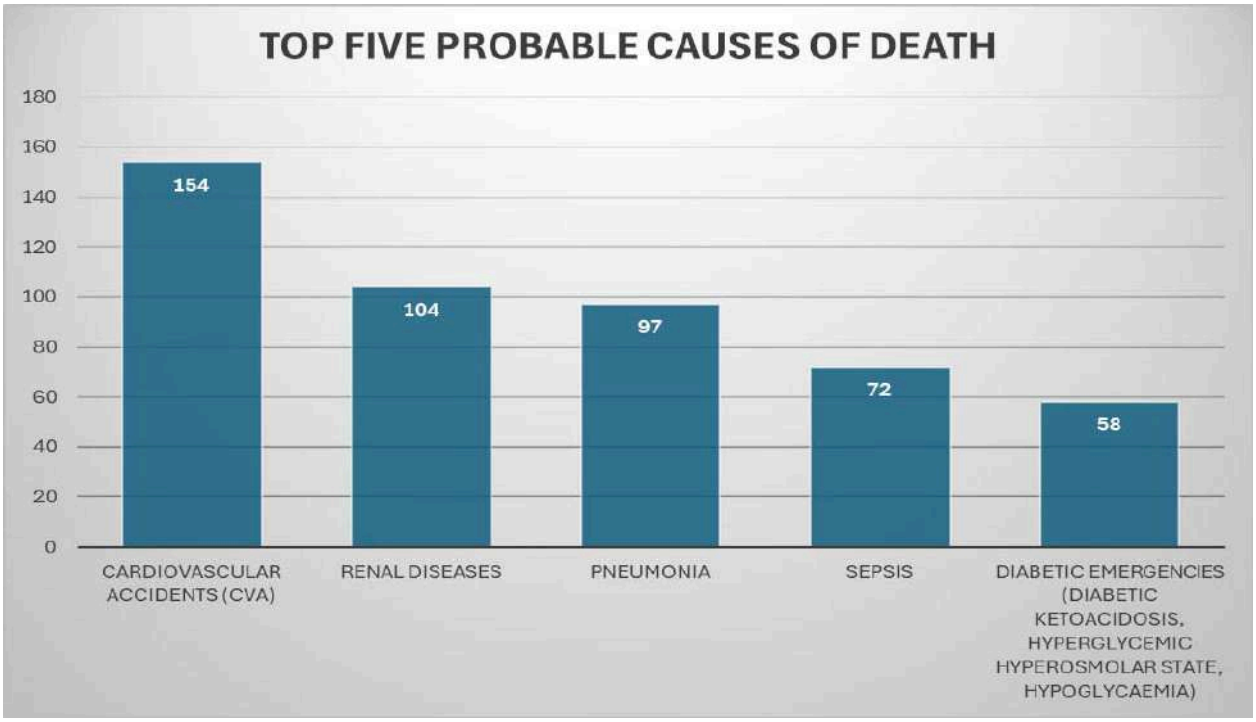


Figure 2: The top five clinical causes of mortality

Table 4: The top five causes of death within 24 hours of admission

	Cause of Death	Number
1	Cerebrovascular Accidents (CVA)	67
2	Pneumonia	65
3	Renal Diseases	48
4	Sepsis	41
5	Hypertensive Emergencies	33

"Modulation of Elevated Triglycerides and Mild NAFLD using Targeted Frequency Bioelectronic Therapy: A Case Study in a Young Healthy Male"

Dott. Daniele Orlandoni & Prof. Giuseppe Di Fede

INTRODUCTION

Triglycerides (TG), together with total cholesterol (Chol-T) as well as high and low- density lipoproteins (HDL, LDL), are lipids of fundamental importance for determining cardiovascular risk (Henein M.Y., 2023). TG are molecules composed of a glycerol nucleus and three fatty acids, fats that we can find in both animal and vegetable foods. They represent the main form of storage and transport of fatty acids within cells and in the plasma, while it is in the liver that the fundamental steps for the metabolism of fatty acids occur (Strable M.S, 2010). Levels of TG higher than 150 mg/dl fasting are characteristic of a state of dyslipidemia (Pappan N. et al., 2024), which can result from a hereditary condition or an incorrect lifestyle; however, this is a condition that, if left untreated, can over time lead to severe cardiovascular consequences or to non-alcoholic fatty liver disease (NAFLD) (Alves- Bezerra M., 2019).

Keywords: NA

Classification: NLM Code: WD200, QU85, QT34

Language: English

LJP Copyright ID: 392845

Great Britain Journals Press

London Journal of Medical & Health Research

Volume 25 | Issue 6 | Compilation 1.0

"Modulation of Elevated Triglycerides and Mild NAFLD using Targeted Frequency Bioelectronic Therapy: A Case Study in a Young Healthy Male"

Dott. Daniele Orlandoni[α] & Prof. Giuseppe Di Fede[σ]

Author α σ: Director of IMBIO (Institute of Biological Medicine).

I. INTRODUCTION

Triglycerides (TG), the most common dietary fats, are molecules composed of a glycerol nucleus and three fatty acids, these fats can be found in both animal and plant-based foods. In the human body TG are the main source of stored energy and together with total cholesterol (Chol-T) and high and low-density lipoproteins (HDL, LDL), are considered lipids of fundamental importance for determining cardiovascular risk (*Henein M.Y., 2023*).

TG also represent the main form of storage and transport of fatty acids within cells and in the plasma as well, while it is in the liver that the latter accumulates through hepatocellular uptake from the plasma and through de novo biosynthesis (*Strable M.S., et al. 2010*). Fatty acids are then eliminated either by oxidation within the cell or secretion into the plasma as triglyceride-rich, very low-density lipoproteins (VLDL).

Physiologically, the liver stores only small amounts of TG still, in the context of overnutrition and obesity, hepatic fatty acid metabolism becomes altered, leading to TG accumulation within hepatocytes and the development of a clinical condition known as non-alcoholic fatty liver disease (NAFLD) (*Alves-Bezerra M. et al., 2019*).

While diet is the primary exogenous source of TG, endogenous TG is synthesized in the liver; triglyceride levels above 150 mg/dl fasting (*Laufs U., 2020*) are characteristic of a condition of dyslipidemia which, from mild to moderate, i.e. 175-885 mg/dl (*Hegele R.A., 2014*), is not only quite common in adults (*Dron J.S., 2019*) but is increasing (*Retterstol K, 2017; Truthmann J, 2016*), together with obesity and type 2 diabetes (Laufs U., 2020). On the other hand, severe HTG (*Bashir B., 2023*), therefore rare, is characterized by a plasma concentration of TG>1000 mg/dl, resulting from a complex genetic basis, which represents an important and known risk factor for acute pancreatitis (*Yuan G., 2007*).

TG levels above 150 mg/dl often result from a lifestyle associated with alcohol intake, a diet rich in refined carbohydrates that can lead to insulin resistance with a consequent increase in circulating TG levels; this is a condition that, if left untreated, can over time lead to serious consequences from a cardiovascular (CV) point of view, as demonstrated by data from numerous epidemiological studies that have highlighted how high TG levels are associated with an increase in CV risk (*Boullart A.C. et al., 2012*). Conversely, it has been demonstrated that lowering TG is associated with a reduced CV risk in patients with high basal TG levels (*Miller M. et al., 2011*).

Based on what has emerged (*Budoff M., 2016*), we can affirm that elevated TG levels can be considered not only a biomarker of CV risk, but also that TG and triglyceride-rich lipoproteins (TRL) are in the causal pathway of atherosclerotic CV disease (ASCVD), and that they play a pathogenic role in atherosclerosis. Furthermore, a condition of dyslipidemia, although mild, can lead to a condition of NAFLD, which has become the most widespread cause of chronic liver disease in the world (*Guo X. et al., 2022*).

1.1 Traditional Approach

Currently, to normalize TG levels, in patients with dyslipidemia, fibrates (*Spence J.D., 2020*),

statins, or statins and ezetimibide (*Ferri N., 2023*) are administrated. With regard to statins, It is important to underline there is poor adherence to their intake by patients (*Stroes E.S., 2015*) due to the muscular symptoms that they cause (*Laufs U., 2015*): about half of them, in fact, interrupt the therapy after 12-24 months (Mann D.M., 2010).

In non-severe forms of hypertriglyceridemia (HTG), supplements based on Omega-3 (*Rodriguez D., 2022; Dewey, F.E., 2017; Nordestgaard, B.G., 2014*) or berberine (*Osadnik T., 2022*) and silymarin (*Li S. et al., 2024*), diet (*Hyun Suk Lee, 2021*) and physical exercise (*Petridou A., 2022*) are also recommended.

Finally, if until a few years ago, NAFLD was a little-known topic, today it is the object of great attention from researchers due to its impact on health since it has become the most commonly found cause of chronic liver inflammation worldwide (*Guo X. et al., 2022*). Furthermore, it should be emphasized that in NAFLD, steatosis is present in more than 5% of hepatocytes with metabolic risk factors such as obesity and type 2 diabetes (*Chalasani N. et al., 2012; Miller M. et al., 2011*).

Since no pharmacological therapy of proven efficacy for NAFLD (*Friedman S.L. et al., 2018*), natural remedies are used, including silymarin (*Guo X. et al., 2022*).

1.2 Bioelectronic Approach

Medical bioelectronics (BEM) refers to the therapeutic modulation of pathological conditions via the stimulation of electrically active tissues, eliciting local or systemic effects through the surgical implantation of bioelectronic devices within the body (*Koutsouras A.D. et al., 2024*).

This field of research is expanding enormously by developing therapeutic opportunities aimed at an ever-increasing number of pathologies such as urological ones (Peregrine B.O., 2017), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and other chronic inflammatory diseases (Genovese et al., 2020, Koopman et al., 2016, Bonaz et al., 2016, Sinniger et al., 2020), Current applications of bioelectronic medicine (BEM) rely on the implantation of medical device technologies designed to modulate—either by amplification or suppression—the activity of the nervous system. Despite their therapeutic potential, these devices can induce an inflammatory response by the surrounding tissues to the electrode materials, known as the Foreign Body Reaction (FBR), an inevitable process triggered by the presence of foreign materials within the body (*Carnicer-Lombarte A. et al., 2021*).

The approach utilizing the BioLife-Regen frequency generator does not require surgical implantation, thereby eliminating the risk of FBR. The procedure involves the non-invasive application of four surface electrodes connected to the device, through which specific regenerative frequencies are transmitted to the body. In this study, we applied the principles of BEM to address a condition characterized by functional alterations in lipid metabolism.

The method used for treatments with the BioLife-Regen frequency generator does not require any implant, thus eliminating the problem of FBR, since it is limited to the application on the body of four electrodes connected to the device, through which to transmit precise regenerating frequencies.

In our research, we used the principles of BEM to correct a condition of functional alteration of lipid metabolism.

1.3 Purpose of the Study

This study aimed to evaluate the effects of a frequency generator, which delivers a fixed and selectively active frequency according to the Grabovoj method (*Grabovoj G., 2013*), in conjunction with supplementation of silymarin, berberine, and Omega-3, on the regeneration of TG levels in a healthy, young male with non-physiological TG values, insufficient to warrant pharmacological intervention. The primary objective was to induce a natural rebalancing of TG metabolism and assess its potential effects on a mild case of NAFLD

(Ultrasound report A). Additionally, we aimed to determine whether the observed changes in TG levels and mild NAFLD could be correlated with alterations in Chol-T, HDL, LDL, and glucose (GLU) levels, in order to assess the specific selective action of the regenerating frequency used.

1.4 Study Subject

The study involved a 19-year-old male subject, healthy, practicing intense competitive physical activity, who at a preventive check-up showed TG values higher than what could be expected in a healthy, young man (Report 1).

Furthermore, a subsequent liver ultrasound revealed a pattern consistent with mild NAFLD (Ultrasound Report A). Nutritional intervention was initiated by first limiting the intake of whole grain carbohydrates to 50–70 g/day, and by *recommending the consumption of the following:*

- *Fats:* coconut oil and clarified butter for breakfast and lunch, extra-virgin olive oil (EVO) for dinner and always for the raw dressing;
- *Fiber:* raw vegetables (for lunch) and legumes (cooked for dinner);
- Fish (especially blue fish);
- White meat;
- 1 low glycemic index fruit per day.
- In addition to this, and to the treatments with the BEM device, it was recommended:
- *Omega-3:* 1500 mg/day (EPA 750 mg+DHA 450 mg+DPA 90 mg), two pearls during lunch and dinner;
- *Berberine:* 500 mg/day;
- *Silymarin:* 105 mg/day.

II. MATERIALS AND METHODS

The BioLife-Regen device (Arpamed Industries; CE-compliant) employed in this study is a frequency generator equipped with a biofeedback and data reacquisition circuit, operated via dedicated external software. The device delivers an electrical signal with predefined parameters, which is transmitted to the human body through surface electrodes.

For the treatment sessions, the device was configured to generate a specific frequency of 5.148.212,00 Hz, as described by Grabovoj (2013), with a current output limited to 25 μA and a 12 V triangular waveform. Each application lasted 15 minutes.

Four 16 cm^2 conductive gel electrode pads were placed on the patient: two in correspondence with the folds inside the wrists and two in the hollow between the medial malleolus and calcaneus. The device was connected to the subject by four 2.0 m long cables; each cable is made up of 259 strands, each 0.07 mm in diameter, with a contact resistance of 40 mOhm and a length of 200 cm, sheathed in silicone in following the IEC61010 standard.

The signal generated by the frequency generator is transmitted along six different paths to ensure correct action on each part of the body by simultaneously transmitting the signal along two channels that remain completely independent throughout the treatment phase, consisting of two identical frequency generator cards powered by a special circuit that receives a 24-volt power supply, which in turn receives 220-volt power from the main electrical supply, with Double Means of Patient Protection (2xMOPP) under the IEC-60601-1 electrical safety standard to ensure adequate electrical isolation of the patient from potential electrical hazards.

Defined as (A) left wrist, (B) right wrist, (C) left ankle, (D) right ankle, the circuits used were for channel-one (CH1) and channel-two (CH2), respectively (Box 1):The treatment phase, which is the subject of this work, was carried out with the following parameters (Box 2):

CH1	CH2
A-B	D-C
C-A	B-D
D-A	C-B
B-C	A-C
A-D	C-D
C-A	D-B

Box 1: Circuits used by the Biolife Regen Device through Connection with the Electrodes Connected to the Patient

The treatment phase, which is the subject of this work, was carried out with the following parameters (Box 2):

Waveform: Triangular.

Minimum voltage: 0 volts.

Maximum voltage: 12 volts.

Frequency: 5.148.212,00 Hz.

Time: 6 x 150 seconds.

Circuits: 6 circuits shown.

Box 2: BioLife-Regen Device Parameters for Treatments according to the Grabovoj Method

2.1 Supplements

The first phase, a combination of 500 mg of berberine from dry extract (E.S.) of Berberis aristata and 100 mg of silymarin from Milk thistle ES. was administered once a day, and Omega-3 in pearls at a rate of 856 mg of EPA and 386 mg of DHA divided into two administrations per day, corresponding to the main meals, for 5 months.

Silymarin has been traditionally used in the treatment of hepatitis (*Pradhan, S.C., 2006*), and has been extensively studied for its hepatoprotective, detoxifying, antioxidant, anti-inflammatory, antidiabetic, and anticancer properties (*Wadhwa K. et al., 2022*). Berberine, on the other hand, is well known for its lipid-lowering effects, particularly in reducing Chol-T and TG levels (*Osadnik T. et al., 2022*).

Omega-3 fatty acids are also employed in clinical practice to reduce CV risk (*Bornfeldt K.E., 2021*), primarily due to their ability to lower plasma TG levels. This effect is thought to result from enhanced fatty acid oxidation, which suppresses hepatic lipogenesis (*Shearer G.C. et al., 2012; Oscarsson J., Hurt-Camejo E., 2017*), thereby reducing the hepatic production of very low-density lipoproteins (VLDL). However, the precise mechanisms by which Omega-3 fatty acids lower TG levels remain incompletely understood.

III. RESULTS

In November 2022 (Table 1; Report 1), the first routine evaluation of TG, Chol-T, HDL, LDL, and GLU levels was conducted. The results revealed TG values above physiological limits, although not high enough to warrant pharmacological intervention. In the same month, the first liver ultrasound was performed (Ultrasound Report A), revealing a mild condition of NAFLD.

We therefore recommended to the subject the supplements already described both in terms of active ingredients and dosages, as well as subjecting him to a monthly treatment with the frequency generator set with the parameters indicated in Box. 2. After five months (Report 2a/b), the TG value had significantly dropped from 409 to 153 mg/dl; after another four months, without having changed the work plan, the TG levels remained practically unchanged (Report 3), and then increased again, reaching 265 mg/dL (Report 4).

Given this lack of response, we decided to suspend the supplements and continue only with a monthly treatment (from October 2023 to July 2024) with the frequency generator, considering that to return to the physiological values, we would have had to go below 150 mg/dl.

At the follow-up visit conducted on July 2024 (Report 5), the TG level was 102 mg/dl, well below the threshold value. At this point, treatment with the frequency generator was discontinued.

At the end of September 2024 (Report 6), about two months after stopping the treatments, we again requested the dosage of all the parameters initially assessed: the TG levels remained stable without any further external intervention.

An interesting observation pertains to the values of Chol-T, HDL, LDL, and GLU. These parameters showed no significant variation between the initial assessment conducted in November 2022 (Table 1) and the final evaluation at the end of September 2024.

In conclusion, treatment with the BioLife-Regen device, using a fixed frequency according to the Grabovoj method (Box 2), aimed at restoring TG levels to physiological values, did not significantly affect the levels of the other parameters. Therefore, it can be affirmed that the efficacy of the treatment appears to be primarily reflected in the stabilization of TG levels.

A control ultrasound performed on 02/21/2024 (Ultrasound Report B) showed the disappearance of the slight steatosis and the restoration of a physiological condition.

Tab. 1: Variations Over time of Chol-T, TG, Chol LDL-HDL, GLU, as function of the treatments Performed with Berberine/Silymarin/Omega-3 and Biolife-Regen at First, then replaced by the Device Alone

BioLife-Regen Treatments	Data of Report	TG mg/dL	Chol-T mg/dL	HDL mg/dL	LDL mg/dL	Glu mg/dL	Intervention
5 treatments (1 per month) 5.148.212 Hz 12V, triangular wave 15 min	1-11/11/22	409	201	48	132	94	Berberin+ silimarina+ Om-3+diet+ BioLife-Regen frequency generator
16 treatments (1 per month) 5.148.212 Hz 12V, triangular wave 15 min	2-12/04/23	153	217	68	119	82	
	3-30/10/23	147	204	67	107	92	
	4-09/02/24	265	231	60	134	81	Only BioLife-Regendevice
	5-29/07/24	102					No intervention
	6-28/09/24	106	206	59	132	90	

IV. DISCUSSION

High levels of TG have proven to be an essential CV element as well as representing an ideal condition for developing NAFLD, in this case, given the young age of the subject, in addition to the diet and the simultaneous initial administration of berberine/silymarin/Omega-3 based supplements, we wanted to try an alternative avenue through a series of applications of a specific regenerating frequency for TG levels according to the Grabovoj method, with a BioLife-Regen frequency generator. The results not only demonstrated a significant reduction in TG levels—restoring them within physiological limits-but also resolved the mild NAFLD condition previously identified by the initial ultrasound evaluation (Ultrasound Reports A and B).

Moreover, analysis of the available data (Table 1) shows that Chol-T, HDL, and LDL levels initially decreased during the simultaneous administration of supplements. However, these parameters-unlike GLU-returned to baseline following treatment with the frequency generator alone and remained stable even two months after treatment cessation. This finding represents a key aspect of the study, underscoring the high specificity of the applied frequency in modulating TG levels without significantly altering other metabolic parameters.

These preliminary results support the potential of this non-invasive, side effect–free technique for addressing functional lipid metabolism imbalances, although further investigation is warranted through additional studies.

Ultrasound report A:

polidiagnostico

Dr.ssa Lucy La Torre
Medico Chirurgo
Specialista in Radiodiagnostica

Paziente: [redacted] nato a: [redacted] (20 aa)
Codice fiscale: [redacted]
Residenza: [redacted]
Telefono: np [redacted]

ECOGRAFIA ADDOME COMPLETO

Data 17/11/2022

MOTIVO DELL'ESAME

Ipertrigliciremia

REFERTO

Non liquido libero in addome.
Fegato di dimensioni e morfologia nei limiti, presenta ecostruttura finemente e modicamente più ecogena come per impronta steatosica di grado lieve non evidenti lesioni a carattere focale nel contesto
Colecisti ben distesa alitiasica; non dilatazione delle vie biliari intra ed extraepatiche.
Pervia e di calibro regolare la vena porta che presenta flusso epatopeto.
Milza regolare per ecostruttura presenta diamentro bipolare di 13,5 cm (recente mononucleosi)
Non espansi in loggia pancreatica
Reni in sede, di dimensioni ed ecostruttura nei limiti: non uroliti tecnicamente rilevabili
Non calicopielectasie.
Vescica ben espansa a pareti regolari non si evidenziano formazioni aggettanti nel contesto.
Prostata con volume stimato per via sovrapubica pari a 17 ml
Aorta addominale di calibro nei limiti
No linfoadenomegalie in lombo-aortica

Esame refertato il 17/11/2022

Dr.ssa La Torre Lucy
LTRLCY73C54A262W

Copia conforme all' originale rilasciata in data 15/04/2025

IL RESPONSABILE SANITARIO
STEFANO MOZZANICA
MEDICO CHIRURGO
CAB SRL
Sede Legale:
Via Casati, 147 - 20862 ARCORE (MB)
Cod. Fisc. e P.IVA 03929470130

(Ultrasound report A: No free fluid in the abdomen. Liver of size and morphology within the limits, *presents a fine and moderately more echogenic echostructure as for mild steatosis*, no evident focal lesions in the context. Gallbladder well distended acalculous; no dilation of the intra and extrahepatic bile ducts. Portal vein patent and of regular caliber, presenting hepatopetal flow. Spleen regular by echostructure presents bipolar diameter of 13.5 cm (recent mononucleosis). Not expanded in the pancreatic lodge Kidneys in place, of size and echostructure within the limits: no technically detectable uroliths. No calicopvelectasis. Bladder well expanded with regular walls, no protruding formations are evident in the context. Prostate with estimated volume by suprapubic route equal to 17 ml Abdominal aorta of caliber within the limits.

No lymphadenomegaly in lumbo-aortic.)

Ultrasound Report B

Salute
Prevenzione
Diagnosi
Cura

cab polidiagnostico

Paziente: [redacted] nato a: [redacted] (20 aa)
Codice fiscale: [redacted]
Residenza: [redacted]
Telefono: np [redacted]

Dr. Cristiano Curadi
Medico Chirurgo
Specialista in Radiodiagnostica

ECOGRAFIA ADDOME COMPLETO O APPARATO URINARIO

Data 21/02/2024

MOTIVO DELL'ESAME

Controllo in ipertrigliceridemia

REFERTO

Fegato di normali dimensioni, con profili regolari, con ecostruttura omogenea, con regolare distribuzione dell'albero vascolare e senza alterazioni a focolaio.Colecisti distesa ed alitiasica.
Non dilatazione delle vie biliari intra ed extra epatiche (la via biliare principale presenta calibro di 3 mm).
Il pancreas presenta normali dimensioni, profili regolari, ecostruttura uniforme, senza tumefazioni abnormi.
Non dilatazione del dotto di Wirsung.
Regolare il calibro della vena porta.
Non versamenti ascitici.
Milza in sede, di normali dimensioni , con ecostruttura omogenea e senza alterazioni a focolaio.
Regolare il calibro e il decorso dell'aorta addominale.
Non tumefazioni abnormi in regione retroperitoneale.
Entrambi i reni sono in sede, di normali dimensioni, con ecostruttura conservata.
Non grossolane formazioni litiasiche.
Non idroureteronefrosi bilateralmente.
Vescica ben distesa, con pareti regolari, senza vegetazioni abnormi al suo interno, senza calcoli e senza impronte estrinseche di significato patologico.
La prostata, esaminata con scansioni sovrapubiche presenta normali dimensioni con volume approssiamtivo di circa 19 mm.
Non versamenti liberi in pelvi.

Esame refertato il 21/02/2024

IL RESPONSABILE SANITARIO
STEFANO MOZZANICA
MEDICO CHIRURGO
CAB SRL
Sede Legale:
Via Casati, 147 - 20862 ARCORE (MB)
Cod. Fisc. e P.IVA 0 3 9 2 9 4 7 0 1 3 0

Dr. Curadi Cristiano
CRDCST69L31M052M
Copia conforme all' originale rilasciata in data 15/04/2025

1/8

Visite Specialistiche | Odontoiatria | Medicina dello Sport

(Ultrasound B: *Liver of normal size, with regular profiles, with homogeneous echostructure, with regular distribution of the vascular tree and without focal alterations*. Gallbladder distended and acalculous. No dilation of the intra and extra hepatic bile ducts (the main bile duct has a caliber of 3 mm). The pancreas has normal dimensions, regular profiles, uniform echostructure, without abnormal swellings. No dilation of the Wirsung duct. Regular caliber of the portal vein. No ascitic effusions. Spleen in place, of normal size, with homogeneous echostructure and without focal alterations.

Regular caliber and course of the abdominal aorta. No abnormal swellings in the retroperitoneal region. Both kidneys are in place, of normal size, with preserved echostructure. No coarse lithiasic formations. No bilateral hydroureteronephrosis.

Bladder well distended, with regular walls, without abnormal vegetations inside it, without stones and without extrinsic imprints of pathological significance.

The prostate, examined with suprapubic scans, presents normal dimensions with an approximate volume of about 19 mm. No free effusions in the pelvis.)

Report 1:

Codice Lab. 2022 98 47454 del 11-11-2022 ore : 07:30
Richiesta : 6439932

BC508 PREVIMEDICAL SPA (DIRETTA)
(A40)
Pagina 1 di 1

Esame	Risultato	U.M.	Valori di riferimento
GLICEMIA *Metodo ENZIMATICO ESOCHINASI [S]*	94	mg/dL	60 - 100 Neonati : 40 - 60 Bambini : 60 - 100 Adulti : 60 - 100
EMOGLOBINA GLICOSILATA (HbA1c) *Metodo HPLC [SI]*			
EMOGLOBINA GLICOSILATA (HbA1c)	5,2	% Hb Totale	<6,5
EMOGLOBINA GLICOSILATA (HbA1c - IFCC)	33	mmol/mol	<48
COLESTEROLO TOTALE *Metodo ENZIMATICO COLORIMETRICO [S]*	201	mg/dL	Fino a 200 * <200 Basso rischio (desiderabile) 200 - 239 Rischio moderato (borderline) >= 240 Alto rischio
COLESTEROLO HDL *Metodo ENZIMATICO [P]*	48	mg/dL	>= 60 Basso rischio (desiderabile) <40 Alto rischio
COLESTEROLO LDL *Metodo ENZIMATICO [P]*	132	mg/dL	Fino a 129 * <100 Livello ottimale 100 - 129 Vicino al livello ottimale 130 - 159 Valore limite alto 160 - 189 Elevato >= 190 Molto elevato
TRIGLICERIDI *Metodo ENZIMATICO COLORIMETRICO [S]*	409	mg/dL	Fino a 150 * Normale : Fino a 150 Borderline alto : 150 - 199 Alto : 200 - 499 Molto alto : > 500
OMOCISTEINA *Metodo CHEMILUMINESCENZA [P]*	9,3	µmol/L	3,7 - 13,9

Referto firmato digitalmente da Dr/Dr.ssa :ROSSELLA VIGNOLA il 11-11-2022 ore 14:07

Per il Direttore Responsabile
Dr.ssa Cristina Kullmann

Referto sottoscritto con firma digitale ai sensi degli artt.20,21 n.2,23 e 24 del D.Lgs n.82 del 7 marzo 2005 e successive modifiche.
I risultati del presente referto trovano la loro efficacia diagnostica se interpretati dal proprio Medico.

Synlab Italia sede Monza
Via Beato Lodovico Pavoni 16 | Castenedolo (BS) | Direttore Laboratorio: Dott.ssa Cristina Kullmann
Ragione Sociale: Synlab Italia S.r.l., soc. unipersonale, Via Martiri delle Foibe 1, 20900 Monza (MB)
Soggetta a Direzione e Coordinamento di Synlab AG

B.C.S. Priamo ver.28

Sistema Sanitario Regione Lombardia

Report 2:

Codice Lab. 2023 40 12552 del 12-04-2023 ore : 07:43
Richiesta : 6874518

ACBARZ BARZANO'
(A40)

Esame	Risultato	U.M.	Valori di riferimento
ESAME EMOCROMOCITOMETRICO *Metodo CITOMETRICO IN FLUORESCENZA - IMPEDENZIOMETRICO [SI]*			Ragazzi 18-19 anni
Globuli Bianchi (WBC)	4,95	10^9/L	4,00 - 10,00
Globuli Rossi (RBC)	5,26	10^12/L	4,70 - 5,82
Emoglobina (HBG)	150	g/L	140 - 170
Ematocrito (HCT)	46,2	%	43,1 - 51,5
Volume corpuscolare medio (MCV)	87,8	fL	81,8 - 95,3
Contenuto Medio Hgb (MCH)	29	pg	27 - 32
Concentrazione Media Hgb (MCHC)	325	g/L	314 - 359
Distribuzione Volume Eritrocitario (RDW)	12,8	%	11,9 - 14,4
Piastrine (PLT)	214	10^9/L	150 - 400
Volume Piastrinico Medio (MPV)	11,6	fL	9,5 - 12,3
FORMULA LEUCOCITARIA			
Granulociti Neutrofili	45,7	%	
Linfociti	41,4	%	
Monociti	9,3	%	
Granulociti Eosinofili	3,0	%	
Granulociti Basofili	0,6	%	
Granulociti Neutrofili	2,26	10^9/L	2,00 - 7,00
Linfociti	2,05	10^9/L	1,10 - 4,00
Monociti	0,46	10^9/L	0,25 - 0,80
Granulociti Eosinofili	0,15	10^9/L	0,00 - 0,50
Granulociti Basofili	0,03	10^9/L	0,00 - 0,10
GLUCOSIO *Metodo ENZIMATICO ESOCHINASI [P]*	82	mg/dL	70 - 100
GLUCOSIO POST-PRANDIALE PRECOCE *Metodo ENZIMATICO ESOCHINASI [P]*	83	mg/dL	

Report 3:

Codice Lab. 2023 40 12552 del 12-04-2023 ore : 07:43
Richiesta : 6874518

ACBARZ BARZANO'
(A40)

Esame	Risultato	U.M.	Valori di riferimento
CREATININEMIA *Metodo JAFFE' [S]*	0,91	mg/dL	0,70 - 1,30
	80	µmol/L	62 - 115
STIMA DEL FILTRATO GLOMERULARE	122	mL/min /1,73m2	

Nota:Utilizzata formula CDK-EPI per il calcolo dell'eGFR.

I risultati ottenuti col metodo di Jaffè non sono riferibili a quelli ottenuti con metodi definitivi. Il calcolo non è applicabile in gravidanza, nei soggetti defedati, con patologie multiple, al di sotto dei 18 anni e oltre i 75 anni.

Tabella di Classificazione dell'IRC della Kidney Disease Quality Initiative

STADIO	GFR	DESCRIZIONE
1	>=90	GFR nei limiti
2	60 - 89	Lieve diminuzione GFR
3A	45 - 59	Modesta diminuzione GFR
3B	30 - 44	Moderata diminuzione GFR
4	15 - 29	Marcata diminuzione GFR
5	< 15	Insufficienza renale-uremia

NOTA:Negli stadi 1-2-3A-3B si può sospettare un danno renale ove sussista:albuminuria persistente,proteinuria persistente,ematurie persistenti(escluse cause urologiche), imaging di anomalie strutturali del rene,glomerulonefrite dimostrata istologicamente.
Pazienti con GFR tra 60 e 89 senza danno renale sono da considerarsi esenti da IRC.

AMILASEMIA *Metodo ENZIMATICO IFCC 37°C [S]*	60	U/L	< 118
LIPASI *Metodo ENZIMATICO COLORIMETRICO [S]*	27	U/L	12 - 53
COLESTEROLO TOTALE *Metodo ENZIMATICO COLORIMETRICO [S]*	217	mg/dL	< 200 desiderabile *
COLESTEROLO HDL *Metodo ENZIMATICO [S]*	68	mg/dL	> 40
COLESTEROLO LDL *Metodo ENZIMATICO [S]*	119	mg/dL	Valore desiderabile < 116

Report 4:

cab polidiagnostico

Glab analisi cliniche

[redacted]

24-013250 .-BARZANO

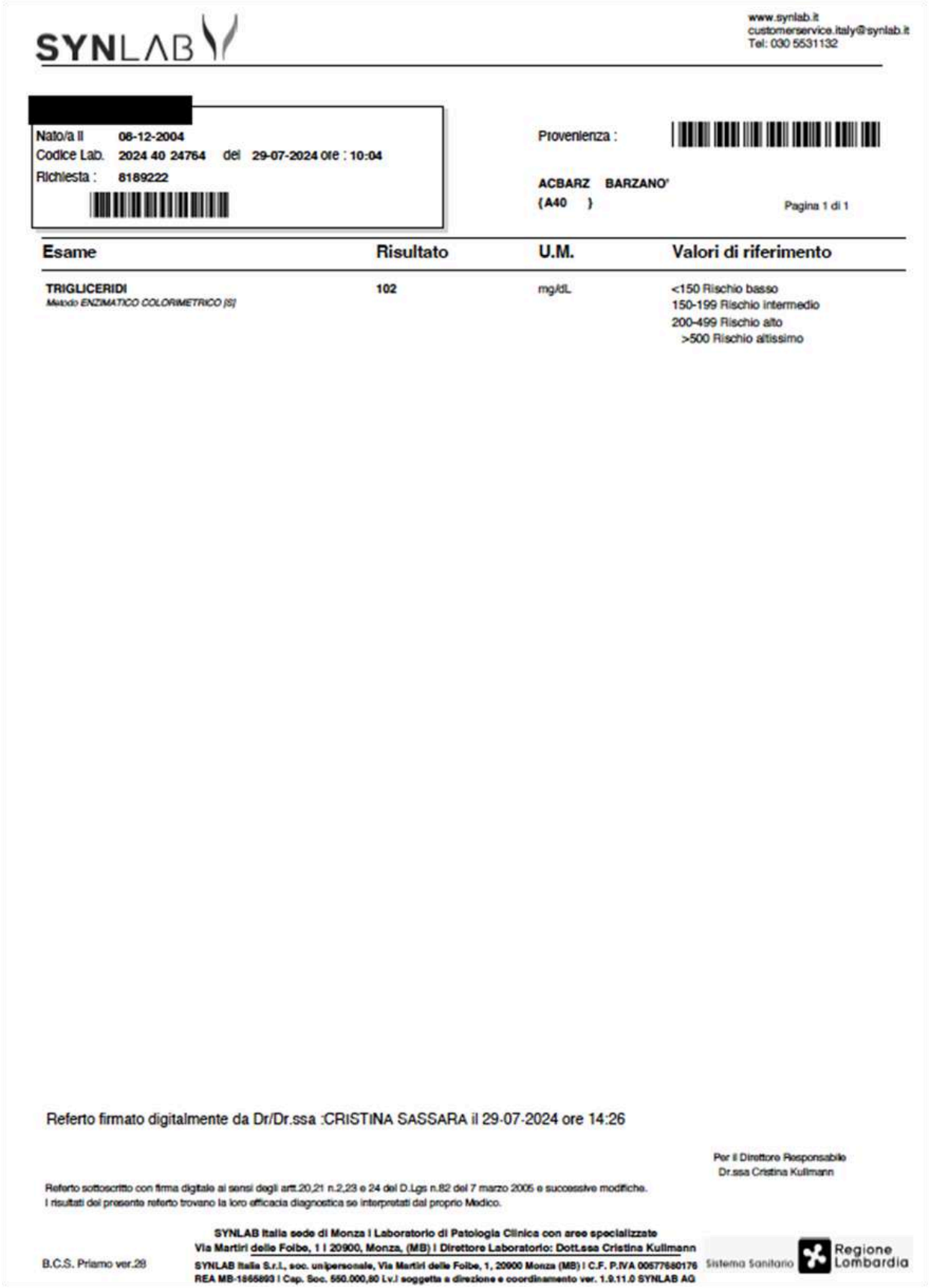
Data prelievo	Richiesta n°	Referto n°	Data ora referto
09/02/2024	24-019126	24-013250	09/02/2024 15:15

Data di nascita	Età	Sesso	CoCli
08/12/2004	19	M	PREVIMEDICAL

Provenienza — Medico richiedente

Analisi	Risultati	U. M.	Valori di riferimento		
GLICEMIA [P] Metodo: COLORIMETRICO	81	mg/dl	70 - 100		
EMOGLOBINA GLICATA (HbA1c) Metodo: HPLC	37	mmol/mol	25 - 46		
	5,5	% Hb Totale	4,4 - 6,4		
COLESTEROLO TOTALE [S] Metodo: ENZIMATICO	231	mg/dl	< 200 200 - 239 > 240	Desiderabile Borderline Alto	*
COLESTEROLO HDL [S] Metodo: ENZIMATICO COLORIMETRICO	60	mg/dl	< 40 40 - 60 > 60	basso intermedio ottimale	
COLESTEROLO LDL [S] Metodo: COLORIMETRICO	134	mg/dl	> 190 160 - 189 130 - 159 100 - 129 < 100	molto alto alto intermedio borderline ottimale	
TRIGLICERIDI [S] Metodo: ENZIMATICO	265	mg/dl	150 - 199 200 - 499 > 500	Borderline alto Alto Molto alto	*

Report 5:



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Nato/a il 08-12-2004
Codice Lab. 2024 40 24764 del 29-07-2024 ore : 10:04
Richiesta : 8189222

Provenienza :

ACBARZ BARZANO'
(A40)

Pagina 1 di 1

Esame	Risultato	U.M.	Valori di riferimento
TRIGLICERIDI *Metodo ENZIMATICO COLORIMETRICO [S]*	102	mg/dL	<150 Rischio basso 150-199 Rischio intermedio 200-499 Rischio alto >500 Rischio altissimo

Referto firmato digitalmente da Dr/Dr.ssa :CRISTINA SASSARA il 29-07-2024 ore 14:26

Per il Direttore Responsabile
Dr.ssa Cristina Kullmann

Referto sottoscritto con firma digitale ai sensi degli artt.20,21 n.2,23 e 24 del D.Lgs n.82 del 7 marzo 2005 e successive modifiche.
I risultati del presente referto trovano la loro efficacia diagnostica se interpretati dal proprio Medico.

B.C.S. Priamo ver.28

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REA MB-1865893 | Cap. Soc. 550.000,80 i.v.| soggetta a direzione e coordinamento ver. 1.9.11.0 SYNLAB AG

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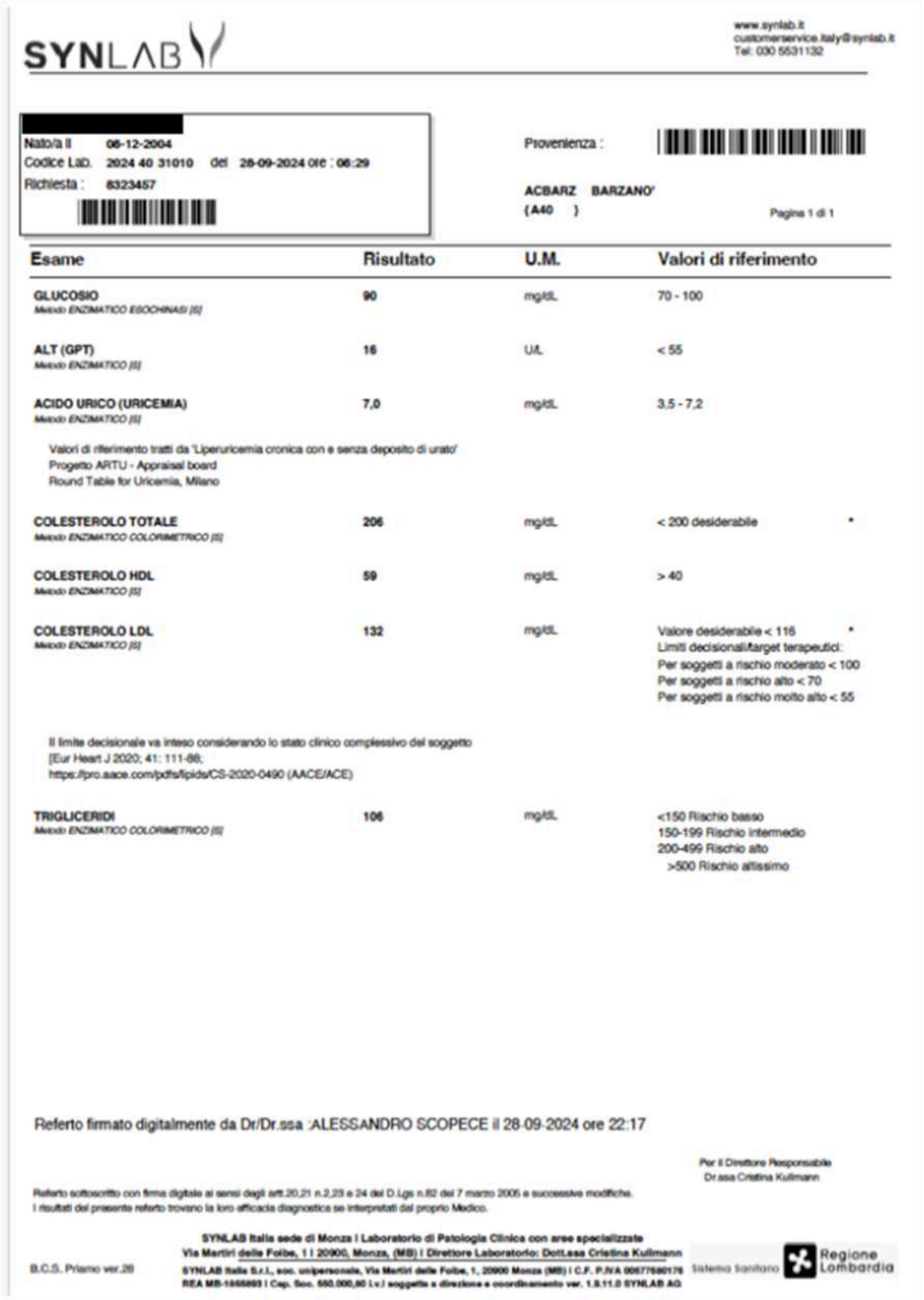
Report 6:



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Nato/a il 06-12-2004
Codice Lab. 2024 40 31010 del 28-09-2024 ore : 06:29
Richiesta : 8323457

Provenienza :

ACBARZ BARZANO'
(A40)

Pagina 1 di 1

Esame	Risultato	U.M.	Valori di riferimento
GLUCOSIO *Metodo ENZIMATICO ESOCHINASI [S]*	90	mg/dL	70 - 100
ALT (GPT) *Metodo ENZIMATICO [S]*	16	U/L	< 55
ACIDO URICO (URICEMIA) *Metodo ENZIMATICO [S]*	7,0	mg/dL	3,5 - 7,2
Valori di riferimento tratti da 'Iperuricemia cronica con e senza deposito di urato' Progetto ARTU - Appraisal board Round Table for Uricemia, Milano			
COLESTEROLO TOTALE *Metodo ENZIMATICO COLORIMETRICO [S]*	206	mg/dL	< 200 desiderabile *
COLESTEROLO HDL *Metodo ENZIMATICO [S]*	59	mg/dL	> 40
COLESTEROLO LDL *Metodo ENZIMATICO [S]*	132	mg/dL	Valore desiderabile < 116 * Limiti decisionali/target terapeutici: Per soggetti a rischio moderato < 100 Per soggetti a rischio alto < 70 Per soggetti a rischio molto alto < 55
Il limite decisionale va inteso considerando lo stato clinico complessivo del soggetto [Eur Heart J 2020; 41: 111-88; https://pro.aace.com/pdfs/lipids/CS-2020-0490 (AACE/ACE)]			
TRIGLICERIDI *Metodo ENZIMATICO COLORIMETRICO [S]*	106	mg/dL	<150 Rischio basso 150-199 Rischio intermedio 200-499 Rischio alto >500 Rischio altissimo

Referto firmato digitalmente da Dr/Dr.ssa :ALESSANDRO SCOPECE il 28-09-2024 ore 22:17

Per il Direttore Responsabile
Dr.ssa Cristina Kullmann

Referto sottoscritto con firma digitale ai sensi degli artt.20,21 n.2,23 e 24 del D.Lgs n.82 del 7 marzo 2005 e successive modifiche.
I risultati del presente referto trovano la loro efficacia diagnostica se interpretati dal proprio Medico.

B.C.S. Primo ver.29

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