Critical Evaluation of the Association Between Elevated Mean Corpuscular Volume and Alcohol-Related Traffic Accidents: A Retrospective Study on 6244 Car Crash Cases

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Background: Erythrocyte mean corpuscular volume (MCV) has been used for decades as a biomarker of chronic alcohol abuse and in the treatment of alcohol dependence. More recently, it has also been adopted to investigate the fitness of subjects to hold the driving license to prevent traffic accidents. So far, however, the studies on the association of MCV with an increased risk of alcohol-associated car accidents are extremely scarce, if not totally absent. To the best of our knowledge, the present work is the first specifically aimed at studying a plausible association between elevated MCV and crash accidents correlated with alcohol abuse.

Methods: A total of 6,244 drivers involved in traffic accidents underwent mandatory laboratory analyses including blood alcohol concentration (BAC) determination and MCV analysis. BAC and MCV determinations were performed by headspace gas chromatography and complete blood count, respectively.

Results: The chi-square test evaluating the proportions of subjects with elevated MCVs (>95 fl) yielded a highly significant result ($\chi^2 = 68.0; p < 0.001$) in the blood samples where the BAC was above the legal limit (i.e., >0.5 g/l). However, when considering only drivers showing BACs in the range of 0.51 to 1.5 g/l, the frequencies of elevated MCV values are fairly comparable ($\chi^2 = 0.062, p = 0.80$). In contrast, limiting the evaluation to BACs >1.5 g/l, the frequency of elevated MCVs raised to 19.1% ($\chi^2 = 58.9, p \text{ value} < 0.001 \text{ vs. the group with BAC within the legal limits}$).

Conclusions: The present observations show that MCV increases are typically associated with drivers involved in accidents only if driving under severe alcohol intoxication, leading to a preliminary conclusion that, in the context of the certification of the fitness to the driving license, MCV fails to reveal individuals at risk who tend to drive in a condition of low-to-moderate alcohol intoxication.

Key Words: Mean Corpuscular Volume, Blood Alcohol Concentration, Alcohol-Related Traffic Accident, Driving License, Drunk Driving.

Since the 1960s, with the fundamental “Grand Rapids Study” (a case-control study carried out in Michigan, USA, in 1964) (Borkenstein et al., 1974; Peden et al., 2004; Walker, 2000), the concern on the alcohol-related traffic accidents and their consequences on the individuals’ health and on the society has led to actions aimed at contrasting driving under the influence (DUI) of alcohol. In this context, legal blood alcohol limits have been set in almost every country and this policy is considered a milestone in the efforts to reduce traffic accident-related deaths and disability.

If there is a widespread evidence-based consensus on the correlation between the impairment of the driving ability and the blood alcohol concentration (BAC), much weaker evidence can be found in the current literature on the correlation between the chronic abuse of alcohol and an increased risk of traffic accidents. It should be stressed that this point is of the highest importance, particularly when individuals, whose driving license has been withdrawn for “drunk driving,” apply for the regranting of their license, pretending to have ceased the abuse of alcohol. In most countries, this delicate matter is under the responsibility of specialized medical committees, who have the task to verify, in any individual, the reality of the alleged abstinence from alcohol. In addition, the medical committee should exclude any reasonable risk of relapse to alcohol abuse and consequently any risk of “driving while intoxicated” in the near future.

Traditionally, the approach to this difficult problem was merely based on medical visits, patient interviews, and few
clinical laboratory data, including liver enzymes and mean corpuscular volume (MCV).

More recently, in most European countries, new biomarkers have been adopted to objectively provide or exclude evidence of chronic alcohol abuse of the subject (Bortolotti and Tagliaro, 2011; Iffland, 1996; Mercier-Guyon, 1996; Musshoff and Daldrup, 1998). Among these biomarkers, carbohydrate-deficient transferrin (CDT) has found wide application (Arndt, 2001; Crivellente et al., 2000; Helander et al., 2003; Lanz et al., 2004; Legros et al., 2003; Schellenberg et al., 2007), with the support of a few studies including retrospective (Appenzeller et al., 2005b; Bianchi et al., 2010; Bortolotti et al., 2007; Brinkmann et al., 2002; Gjerde and Morland, 1987; Iffland and Grassnack, 1995; Iffland et al., 1994; Jaster and Wegener, 1993; Kristenson and Jeppsson, 1998) and prospective (Appenzeller et al., 2005a; Maenhout et al., 2004; Marques et al., 2009; Portman et al., 2010) researches. Also, it has recently been reported that elevated CDT concentrations are associated with an increased risk of DUI and, more importantly, with an increased risk of alcohol-related traffic injuries (Bortolotti et al., 2015).

Notwithstanding distinct advantages of using CDT as a biomarker in driving license regranting programs, the use of this diagnostic parameter shows limitations related to analytical complexity and costs, particularly in countries where Public Health budgets are limited.

In this context, MCV is a standard hematological parameter currently measured at low costs in any hospital laboratory by using sound and reliable technologies. In addition to a number of clinical conditions characterized by macrocytosis, elevated MCV is a typical morphological anomaly caused by excessive consumption of alcohol. As a biomarker of chronic alcohol abuse, MCV has been traditionally used for decades in clinical medicine and in the treatment of alcohol dependence showing a sensitivity ranging from 40 to 80% (Neumann and Spies, 2003) with reported substantial differences between females (86%) and males (63%) (Morgan et al., 1981; Sillanaukee et al., 1998). Other reports pointed out an age-dependent sensitivity to detect alcohol abuse (Caputo et al., 2012; Conigrave et al., 2003). On the other hand, the use of MCV as an alcohol biomarker shows a high diagnostic specificity (over 90%) (Meerkerk et al., 1999; van der Ende et al., 1999; van der Ende and Daldrup, 1998). Among these biomarkers, carbohydrate-deficient transferrin (CDT) has found wide application (Arndt, 2001; Crivellente et al., 2000; Helander et al., 2003; Lanz et al., 2004; Legros et al., 2003; Schellenberg et al., 2007), with the support of a few studies including retrospective (Appenzeller et al., 2005b; Bianchi et al., 2010; Bortolotti et al., 2007; Brinkmann et al., 2002; Gjerde and Morland, 1987; Iffland and Grassnack, 1995; Iffland et al., 1994; Jaster and Wegener, 1993; Kristenson and Jeppsson, 1998) and prospective (Appenzeller et al., 2005a; Maenhout et al., 2004; Marques et al., 2009; Portman et al., 2010) researches. Also, it has recently been reported that elevated CDT concentrations are associated with an increased risk of DUI and, more importantly, with an increased risk of alcohol-related traffic injuries (Bortolotti et al., 2015).

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calculated using GraphROC for Windows, a software program for clinical test evaluation, kindly provided by Dr. Kairisto. The reference intervals were calculated using the C28-A3c CLSI standard (Clinical and Laboratory Standards Institute, Katayev et al. 2010) by the software MedCalc v.18.9 (Odense, Belgium).

Owing to the mandatory feature of the BAC determination, no specific ethical approval was required for blood collection and data use. All data were anonymized before use.

The statistical analysis was carried out using nonparametric methods and particularly the chi-square test and the calculation of odds ratio (OR). OR is a numerical expression which attempts to quantify the strength of the association between two parameters, A and B [OR expresses the ratio of the odds of A in the presence of B to the odds of A without the presence of B]. If the OR is greater than 1, then A is considered to be associated with B in the sense that, compared to the absence of B, the presence of B raises the odds of A.

### RESULTS

The studied population, classified as detailed in the “Materials and Methods” section, shows the following descriptive statistical figures:

- **group A (BAC > 0.5 g/l, n = 2,718):** average MCV = 87.81 fl (SD = 7.17)
- **group B (0.5 < BAC < 1.5 g/l, n = 905):** average MCV = 87.85 fl (SD = 7.06)
- **group C (BAC > 1.5 g/l, n = 2,621):** average MCV = 89.19 fl (SD = 7.07).

[Correction added 20 May 2019. Group B incorrectly listed the values as greater than 1.5 g/l.]

The “chi-square” significance test was first applied to check the “null hypothesis” of absence of difference in the proportions of elevated MCV between the studied groups. Furthermore, the degree of association between the occurrence of elevated MCV values and alcohol-related accidents was evaluated by calculating the odds ratio.

By using the above-mentioned subdivision, the studied cases were classified as in Table 1.

The proportions of subjects with elevated MCVs were 11.6, 11.9, and 19.1% in groups A, B, and C, respectively. The chi-square test yielded a highly significant result ($\chi^2 = 68.0; p < 0.001$). At a closer look, however, it is patent that limiting the comparison to group B versus group A, the frequencies of elevated MCV values are fairly comparable, with no significant difference in the proportions ($\chi^2 = 0.062, p = 0.80$). On the other hand, when considering group C (BAC > 1.5 g/l) for the comparison with group A, the frequency of elevated MCV values raised to 19.1% ($\chi^2 = 58.9; p < 0.001$).

### DISCUSSION

These observations clearly show that MCV is typically increased only in drivers involved in an accident under severe alcohol intoxication. In fact, MCV does not increase in subjects driving with BAC levels above the legal limit but below those associated with the heavier symptoms, that is, >0.5 but ≤1.5 g/l. These findings may lead to a preliminary conclusion that, in the context of the certification of the fitness to the driving license, MCV fails to reveal an important class of individuals at risk, that is, those who tend to drive in a condition of low-to-moderate alcohol intoxication.

When evaluating the strength of the association between the 2 considered factors (BAC at the time of the accident and MCV), an odds ratio of 1.81 was found when comparing the frequencies of elevated MCV values in group C versus group A (the odds were 502/2,119 in group C and 314/2,404 in group A). Despite the significant result associated with this odds ratio (which can be considered significantly different from the “null” value 1.0, meaning no association at all), in our opinion the strength of the association can be considered weak, limiting the practical usefulness of MCV even for the identification of the conditions of the highest risk for the traffic safety.

The present retrospective study, for logistic reasons, has not included other biomarkers of chronic alcohol abuse, such as CDT, which in recent papers have shown an impressively high association with the risk of alcohol-related traffic accidents (Bortolotti et al., 2015). Further studies will be needed to have a deeper insight in this intricate topic.

### CONCLUSIONS

In the last decades, important efforts have been undertaken worldwide with the intent of increasing the traffic safety, particularly by reducing the alcohol-associated traffic accidents. Among these efforts, the adoption of strict procedures for the verification of the fitness to hold the driving license, hindering alcohol abusers from driving vehicles, is one of the most relevant. Unfortunately, neither clinical signs nor biomarkers have, so far, been clearly identified which can undoubtedly indicate that an individual shows an increased risk of being involved in a traffic crash because of their drinking habits. In this context, MCV stands out among the biomarkers of chronic alcohol abuse most traditionally used in the process of certification of the fitness to the driving license. Nevertheless, to the best of our knowledge, notwithstanding its adoption in many countries, the literature is lacking for specific studies on the association between increased MCV values and the occurrence of road accidents. The present study has been aimed at verifying such hypothesis.

A general evaluation of the results of the present retrospective study shows a neat statistical difference in the frequency of elevated MCV values in the blood samples of the drivers in which at the time of the crash the BAC was above the legal limit in comparison with the samples with BAC values within the legal limits. However, when considering only drivers showing BACs between 0.51 and 1.5 g/l, no statistical differences were observed.
difference was found in the frequency of elevated MCV values. On the contrary, limiting the evaluation to BACs > 1.5 g/l, the frequency of elevated MCV values raised to 19.1%. Unfortunately, the degree of the association, quantified by means of the odds ratio, despite the statistical significance, can be considered low for practical purposes.

This clearly leads to a preliminary conclusion that MCV is typically increased only in drivers involved in an accident under severe but not in low-to-moderate alcohol intoxication conditions. Hence, in the context of the certification of the fitness to the driving license, MCV fails to reveal an important class of individuals at risk.

In particular, the low odds ratios of the associations, even when statistically significant, reduce the predictiveity of this parameter and consequently its practical usefulness for certifying the fitness of individuals to hold the driving license.

REFERENCES


