The utility of lung weight to heart weight ratio as a means to identify suspected drug intoxication deaths in a medico-legal autopsy population

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Abstract
Fatal intoxications are common in a medico-legal autopsy setting and are associated with sparse findings during autopsy. It has been suggested that an increased lung weight may be associated with such fatalities. Previous literature is generally limited to a descriptive approach, including only opioid deaths, and lacking a definition of “heavy” lungs. Our aim was to create a model to identify cases with heavy lungs and to assess the predictive power of “heavy” lungs in identifying cases of different types of fatal intoxications during autopsy in an unselected medico-legal autopsy population. We identified all medico-legal autopsy cases ≥18 years in Sweden from 2000 through 2013. The lung weight to heart weight (LWHW) ratio was calculated. The positive predictive values (PPV) and negative predictive values (NPV) of both lung weight and LWHW ratio were calculated. Mean lung weight was higher in the intoxication group but the predictive power in the individual case was limited. Lung weight to heart weight ratio had better predictive power than lung weight alone, with a PPV of at most 0.15 (0.14, 0.16 95% CI), while the NPV was 0.96 (0.95, 0.96 95% CI). The association between fatal intoxication and increased lung weight was positive, regardless of method and cutoffs used. While the PPV was poor, the NPV could reduce suspicion of fatal intoxication in the absence of other information. LWHW ratio is only a probability factor for fatal intoxication; accurate cause of death determination—as always—requires consideration of circumstances, autopsy, and toxicologic findings.

KEYWORDS
autopsy, fatal intoxication, forensic pathology, lung weight, lung: heart weight ratio, opioid, predictive value

Highlights
• The LWHW (lung weight to heart weight) ratio normalizes lung weight to specifically define “heavy lungs.”
1 | INTRODUCTION

Fatal intoxications are prevalent in a medico-legal autopsy setting, constituting approximately 10% of medico-legal autopsies in Sweden (internal data). These cases are difficult to diagnose at autopsy as morphological findings are sparse, although "heavy lungs" has been suggested as a finding indicating fatal intoxication in several studies [1–8]. These studies are, however, (i) mostly limited to opioid deaths, (ii) based on small samples, and (iii) only descriptive and/or compare only mean values of lung weight across different causes of death. A recent study has also examined the relationship between lung weight, brain weight, and "bladder fullness" in 82 cardiovascular and 83 opioid-related deaths [9]. This study found only a modest positive predictive value of 71% for correctly differentiating opioid-related deaths from cardiovascular deaths.

Moreover, though many different reference weights have been suggested, "heavy lungs" still eludes definition [10–16]. There have been attempts at creating linear regression models using individual characteristics to estimate postmortem lung weight [10,12,13,14,16,17]. Apart from one study [10], neither height, weight, age, nor BMI have yielded models of practical use.

A problem with previous studies is also that they generally as control cases include decedents with an obvious external cause of death and/or exclude all cases with confounding factors such as congestive heart failure. This may inflate the effect of any difference detected and ignore the base rate probability of fatal intoxication in a medico-legal autopsy population. We instead suggest that it would be better to assess the utility of such a test in the actual population in which it would be applied.

The aim of this study was to analyze the predictive value of "heavy lungs" for fatal intoxications in a large and unselected medico-legal autopsy population. We also aimed to assess the predictive power of lung weight to heart weight ratio, where the heart weight is assumed to normalize the lung weight to the relative size of the thorax, a method that has been applied with some success in fatal drowning cases [18].

2 | MATERIALS AND METHODS

2.1 | Study population

In Sweden, all medico-legal autopsies are performed at one of six units of forensic medicine at the National Board of Forensic Medicine. Using the national medico-legal autopsy registry, we identified all decedents 18 years and older subjected to an autopsy in the years 2000 through 2013 (n = 71,414). All cases with a postmortem interval exceeding 5 days (n = 42,801), cases without a registered sex (n = 56), cases without a valid registered lung weight (n = 3404), and all cases with extreme height (<120 cm and >250 cm; n = 803), body weight (<20 kg and >300 kg; n = 121), heart weight (<200 g and >1000 g; n = 262), or combined lung weight (<200 g and >5000 g; n = 3) were excluded. In total, 23,978 cases were included.

Cases were categorized using the coded (ICD-9/10, as modified by the Swedish National Board of Forensic Medicine) cause of death as stated on the death certificate (Table 1).

Lung weight was defined as the combined weight of both lungs. "Mass" (the amount of matter in an object, measured in kg) is a more scientifically correct term than "weight" (the mass times the gravitational pull exerted on the object, measured in Newtons). We chose, however, to use the word "weight" as a synonym for "mass" as it is more common in the literature and more readily understandable to the layperson.

| Group                              | ICD-9   | ICD-10  |
|------------------------------------|---------|---------|
| Overall (excluding alcohol)        | 960–979 | T36-50  |
| Fatal intoxication with a single substance | 977K    | NA      |
| Fatal intoxication with multiple substances | 977L    | NA      |
| Fatal intoxication with a single substance and ethanol | 980C    | NA      |
| Fatal intoxication with multiple substances and ethanol | 980L    | NA      |
| Fatal opioid intoxication          | 965A    | T40–40.4|
| Fatal CNS stimulant intoxication   | 969H    | T40.5, T43.6 |
| Fatal antidepressant intoxication  | 969A    | T43.0–43.2 |
| Fatal ethanol intoxication         | 980A    | T51.0   |

Note: that some of these ICD-9 codes are the result of modification by the Swedish National Board of Forensic Medicine for better adaptation to cause of death diagnoses in a medico-legal death population.
2.2 | Methods

The lung weight to heart weight ratio (LWHW ratio) was calculated for each case, and the mean ratio was calculated in the total population and in each stratum of sex and BMI category.

Independent samples t-tests were used to assess whether there were significant differences in mean lung weight between groups.

We identified heavy lungs based on cases where the LWHW ratio was above the mean, both overall and in subgroups based on sex and BMI category.

The applicability of this definition of "heavy lungs" for identifying fatal intoxications was evaluated using sensitivity, specificity, and positive as well as negative predictive values. Since positive and negative predictive values are questionable if the base rate is incorrect (such as in the smaller subgroups), we also calculated positive and negative likelihood ratios, a measurement which is invariant to the base rate. All results are presented with 95% confidence intervals (CI).

The stratified ratio was converted to Z scores, that is, standardized to have a mean of 0 and a standard deviation of 1, allowing us to treat the ratio as a continuous variable common to all subgroups. Further, receiver operating characteristic (ROC) analysis of the best performing models was performed to optimize the sensitivity and specificity of models. Optimal values were calculated using Youden’s J statistic.

Statistical analyses were performed using R 3.6.0.

All analyses were also performed using "classic" analyses, in which all cases with cardiac and/or pulmonary disease on the death certificate were excluded. Cases where the underlying cause of death was asphyxia were chosen as control cases.

Details regarding the included population as well when using asphyxia deaths as controls (Tables S1 and S2), t-tests (Tables S3 and S4), sensitivity, specificity, and associated statistics (Tables S5 and S6), logistic regression results (Figure S1), and ROC plots (Figure S2–S4) can be found in the Appendix S1.

3 | RESULTS

The overall population was predominantly male (74%) and middle-aged (Table 2). The overwhelming number of intoxication cases had a non-specific fatal intoxication cause of death code (1294 out of 2189 non-ethanol intoxication cases, 59%), followed by opioid intoxication cases (448 cases, 20%) and CNS stimulants (58 cases, 2.6%). Intoxication cases overall were slightly younger than the total population, and this difference was more pronounced in the CNS stimulant and opioid intoxication groups. The LWHW ratio decreased with decreasing BMI (Table 3).

On average, the lungs were heavier in deaths due to intoxication compared to controls, with a difference of 159 g (144, 174 g 95% CI). The difference was larger when comparing pure opioid intoxication cases to non-intoxication cases, 235 g (205, 265 g 95% CI).

Using the LWHW ratio stratified for sex and BMI slightly improved the sensitivity and the specificity in identifying cases of fatal intoxication compared to lung weight only (Table 4). In all cases, the negative predictive value was high, in opioid intoxication cases as high as 0.99 (0.99, 0.99 95% CI). The negative likelihood ratio was small to moderate with 0.45(0.41, 0.49 95% CI) in the overall group and 0.31 (0.23, 0.36 95% CI) in the opioid group. A ROC analysis of stratified LWHW ratio showed that the optimal cutoff point was +0.12 SD from the mean for fatal intoxications in general and +0.17 SD from the mean for opioids specifically (see Figure S3 in the Appendix S1 for details).

| TABLE 2 | Lung weight, heart weight, age, body mass index (BMI), and sex by total population and intoxication subgroups |
|----------|---------------------------------------------------------------|
|          | Overall | All fatal intoxications | Fatal opioid intoxications |
| Total population size (n) | 23,978 | 2189 | 448 |
| Combined lung weight (g) (range, SD) | 1229 (200–4318, 378) | 1374 (480–2880, 336) | 1460 (692–2880, 317) |
| Heart weight (g) (range, SD) | 416 (200–1000, 110) | 391 (200–910, 93) | 388 (210–910, 80) |
| Age (years) (range, SD) | 53 (18–102, 18) | 43 (18–95, 17) | 35 (18–83, 11) |
| BMI (mean, SD) | 26 (5) | 27 (6) | 26 (5) |
| Male sex (n, %) | 17,675 (74%) | 1394 (64%) | 387 (86%) |

4 | DISCUSSION

Regardless of method and cutoffs applied to identify” heavy lungs,” the association of lung weight with fatal intoxication cases was positive. While the positive predictive value (i.e., the probability of fatal intoxication if the test is positive) was poor, the negative predictive value (i.e., the probability that a case is not a fatal intoxication given a negative test) was strong enough to reduce a prior suspicion of fatal intoxication. However, this is true only in the cases where there is no additional information available. The model neglects the case history which is often especially important in estimating the degree to which intoxication as cause of death should be suspected. If there was a known history of substance abuse or other findings suggestive of an intoxication death (e.g., needle marks or undigested pills in the stomach), the underlying population would be quite different. The base rate of fatal intoxication in such a subsection is highly likely to be higher than in the study population in this study, possibly increasing the positive predictive value and reducing the negative predictive value.

The positive likelihood ratio (i.e., ratio of true positives to false positives of a given test) was low, in line with the findings of the
positive predictive value. The negative likelihood ratio was low in the overall population and nearing moderate in the opioid group. This implies that all things are equal, and the effect of increased lung weight or LWHW ratio on the probability of fatal intoxication given a moderate or higher suspicion of a drug death is quite minor (see equation 1 and 2 in the Appendix S1 for an elaboration on this subject).

LWHW ratio outperformed other tested models which used lung weight alone, though the difference in likelihood ratios and predictive values were small (Table 4). This is possible because the heart is less prone to fluid build-up, and hence, its weight normalizes the lung weight, enabling us to identify cases where the lung weight is above normal for that individual. The fact that there was a large difference in the performance of lung weight in predicting fatal intoxication when utilizing it in an unselected population as compared to a population with asphyxia deaths as controls seems to support this (see Tables S5 and S6 in the Appendix S1).

Such a simple heuristic is, however, quite limited and neglects many other forms of information that might be relevant in fatal intoxication cases, such as case history, bladder distension, and cerebral edema [9]. While it is possible or even probable that including such information would improve the predictive value of the model, it would also be necessary to be far more complicated and as such harder to implement in forensic practice.

**TABLE 3** Mean lung weight to heart weight ratio (LWHW ratio) (SD) by BMI and sex

| LWHW ratio (SD) | Overall | 3.05 (0.98) |
|-----------------|---------|-------------|
| Men             |         |             |
| Underweight (BMI <18.5) | 3.40 (1.14) | 3.30 (1.06) |
| Normal weight (BMI 18.5–25) | 3.22 (1.07) | 3.22 (1.01) |
| Overweight (BMI 25–30) | 2.96 (0.94) | 2.97 (0.89) |
| Obese (BMI >30) | 2.70 (0.83) | 2.69 (0.79) |

**TABLE 4** Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR⁺), and negative likelihood ratio (LR⁻) of lung weight above mean and of lung weight to heart weight ratio (LWHW ratio) above sex and BMI category stratified mean

| Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | LR⁺ (95% CI) | LR⁻ (95% CI) |
|----------------------|----------------------|--------------|--------------|--------------|--------------|
| LWHW ratio above mean|                      |              |              |              |              |
| All fatal intoxications | 0.74 (0.72, 0.76) | 0.58 (0.57, 0.58) | 0.15 (0.14,0.16) | 0.96 (0.95, 0.96) | 1.76 (1.67, 1.81) | 0.45 (0.41, 0.49) |
| Fatal opioid intoxications | 0.83 (0.80, 0.87) | 0.55 (0.55, 0.56) | 0.03 (0.03, 0.04) | 0.99 (0.99, 0.99) | 1.84 (1.78, 1.98) | 0.31 (0.23, 0.36) |
| Lung weight above mean |                      |              |              |              |              |
| All fatal intoxications | 0.64 (0.62, 0.66) | 0.53 (0.53, 0.54) | 0.12 (0.12, 0.13) | 0.94(0.93, 0.94) | 1.36 (1.32, 1.43) | 0.68 (0.63, 0.72) |
| Fatal opioid intoxications | 0.76 (0.72, 0.80) | 0.53 (0.52, 0.53) | 0.03 (0.03, 0.03) | 0.99(0.99, 0.99) | 1.62 (1.50, 1.70) | 0.45 (0.38, 0.54) |

In our study, the lungs in intoxication deaths were significantly heavier than in non-intoxication deaths, in line with previous studies [1–8]. However, the overall mean lung weight was higher in the present study than most previously reported values [13–15,17]. Indeed, it was higher than many of the previously published mean values for drug-related deaths [1–2,5,7]. This might be because of our inclusion of cases with significant co-morbidity, which increases the average lung weight among non-intoxication cases, driving up the overall average.

### 4.1 Strengths and limitations

This was a retrospective study, and there is a risk of circular reasoning when studying a finding in relation to the cause of death. However, this risk should have minimal importance in the present context, as while the lung weight can inform the forensic pathologist in the interim between the autopsy and the toxicological results, the cause of death is based on the autopsy findings, the toxicological analyses, and the circumstantial evidence in the individual case, never on the lung weight. Hence, the weight of the lungs and the toxicological results are objective mutually independently registered objective findings.

The data included in this study are severely limited as most toxicological causes of death cases are, by tradition, coded using non-specific ICD-9 codes. Although this means that the data are a good estimate of the baseline of fatal intoxication overall (and the major subgroup of isolated opioid intoxication), the base rate of fatal intoxication in the smaller subgroups is questionable. Furthermore, the sample sizes in these groups were quite small, and as such, it remains unclear to which degree drugs other than opioids affect lung weight (see Table S1 in the Appendix S1).

Any model that pools intoxication types might cause issues by increasing the theoretical likelihood of intoxication among “average” cases as the expected lung weight in fatal intoxication victims is decreased, by inclusion of non-opioid intoxication deaths. There
might also be other unknown confounders, such as certain population groups being more prone to be fatally intoxicated. For instance, dece-
dents with some inherent lung sensitivity that perhaps make them more prone to edema may perhaps also be more likely to die of an opioid overdose. The model applied has the obvious drawback that it would automatically deem intoxication less likely among cases with enlarged hearts, a common feature in a medico-legal autopsy setting.

An unselected medico-legal autopsy population was used to estimate normal lung weight and the LWHW ratio, as opposed to a selected population where the lung and heart weights should be “unaffected” by disease or other confounders. We believe that the study population chosen by us is more reflective of the real situation, since the estimated weight and ratio is otherwise valid only in the specifically selected population and as a result will overesti-
mate the difference between controls and intoxication deaths.

The LWHW ratio seems to offer a more appropriate definition of “heavy lungs” and may represent a better approach to identify intox-
ication deaths than lung weight alone. The LWHW ratio is, however, only supportive of the diagnosis of fatal intoxication. All medico-legal cases should include a basic toxicological screening, and the cause of death should of course be based on the circumstances as well as autopsy and toxicological findings.

5 | CONCLUSIONS

In conclusion, there is little evidence to support the use of raw lung weight or LWHW ratio to estimate the probability of fatal intoxica-
tion. The inverse is more practically useful as a low LWHW ratio can, in absence of other information like case history, reduce suspicion of fatal intoxication in the interim between autopsy and toxicological analyses. To account for this lack in case information, future studies are needed where case history as well as other findings as are cat-
ergized and included in expanded predictive models.

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REFERENCES
1. Albion C, Shkrum M, Cairns J. Contributing factors to methadone-
related deaths in Ontario. Am J Forensic Med Pathol. 2010;31(4):313– 9. https://doi.org/10.1097/PAF.0b013e3181ca4b1e.
2. Chen HI-H, de Jong J. Increased lung weights in drug-related fatali-
ties. J Forensic Sci. 2017;62(6):1632– 4. https://doi.org/10.1111/15
56-0429.13452.
3. Force EE, Fisher RS, Millar JW. Epidemiological and ecological study of risk factors for narcotics overdose. IV. Retrospective histopathological study of lungs in cases of fatal narcoticism: com-
parative analysis for potential hypersensitivity reaction. Arch Environ Health. 1973;26(3):111–9. https://doi.org/10.1080/00039
896.1973.10666237.
4. Henderson GL. Fentanyl-related deaths: demographics, circumstances, and toxicity of 112 cases. J Forensic Sci. 1991;36(2):422–33.
5. Karch SB, Stephens B, Ho CH. Relating cocaine blood concentrations to toxicity – an autopsy study of 99 cases. J Forensic Sci. 1998;43(1):41–5.
6. Kringsholm B, Christoffersen P. Lung and heart pathology in fatal drug addiction. A consecutive autopsy study. Forensic Sci Int. 1987;34(1-2):39–51. https://doi.org/10.1016/0379-0738(87)90082-x.
7. Pilgrim JL, McDonough M, Drummer OH. A review of methadone deaths between 2001 and 2005 in Victoria, Australia. Forensic Sci Int. 2013;226(1-3):216–22. https://doi.org/10.1016/j.jforensicint.2013.01.028.
8. Wetti CV, Davis JH, Blackbourne BD. Narcotic addiction in Dade County, Florida. An analysis of 100 consecutive autopsies. Arch Pathol. 1972;93(4):330–43.
9. Molina DK, Vance K, Coleman ML, Hargrove VM. Testing an age-
old adage: can autopsy findings be of assistance in differentiating opioid versus cardiac deaths? J Forensic Sci. 2020;65(1):112–6. https://doi.org/10.1111/1556-4029.14174.
10. de la Grandmain GL, Clairand I, Durigon M. Organ weight in 684 adult autopsies: new tables for a Caucasoid population. Forensic Sci Int. 2001;119(2):149–54. https://doi.org/10.1016/s0379
-0738(00)00401-1.
11. Hadley JA, Fowler DR. Organ weight effects of drowning and as-
phyxiation on the lungs, liver, brain, heart, kidneys, and spleen. Forensic Sci Int. 2003;137(2-3):239–46. https://doi.org/10.1016/
so379-0738(03)00332-3.
12. Mandal R, Loeffler AG, Salamat S, Fritsch MK. Organ weight changes associated with body mass index determined from a medical autopsy population. Am J Forensic Med Pathol. 2012;33(4):382–9. https://
doi.org/10.1097/PAF.0b013e3182518e5f.
13. Molina DK, DiMaio VJM. Normal organ weights in men: part II – The brain, lungs, liver, spleen, and kidneys. Am J Forensic Med Pathol. 2012;33(4):36872. https://doi.org/10.1097/PAF.0b013e318252d9ad.
14. Molina DK, DiMaio VJM. Normal organ weights in women: part II – The brain, lungs, liver, spleen, and kidneys. Am J Forensic Med Pathol. 2015;36(3):182–7. https://doi.org/10.1097/PAF.00000
0000000175.
15. Sheikhazadi A, Sadr SS, Ghadyani MH, Taheri SK, Manouchehri AA, Nazparvar B, et al. Study of the normal internal organ weights in Tehran’s population. J Forensic Leg Med. 2010;17(2):78–83. https://doi.org/10.1016/j.jflm.2009.07.012.
16. Gustafsson T, Eriksson A, Wingren CJ. Multivariate linear regres-
sion modelling of lung weight in 24,056 Swedish medico-legal autopsy cases. J Forensic Leg Med. 2017;46:20–2. https://doi.
or/10.1016/j.jflm.2016.12.001.
17. Peddle L, Kirk GM. Postmortem organ weights at a South African mortuary. Am J Forensic Med Pathol. 2017;38(4):277–82. https://
doi.org/10.1097/PAF.0000000000000340.
18. Tse R, Garland J, Kesha K, Morrow P, Lam L, Elstub H, et al. The potential diagnostic accuracy of autopsy lung weights, lung-heart ratio, and lung-body ratio in drowning deaths. Am J Forensic Med Pathol. 2018;39(3):223–8. https://doi.org/10.1097/PAF.00000
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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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